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Regional analysis of femorotibial cartilage loss in a subsample from the Osteoarthritis Initiative progression subcohort

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Summary

Objective: The Osteoarthritis Initiative (OAI) is aimed at validating (imaging) biomarkers for monitoring progression of knee OA. Here we analyze regional femorotibial (FT) cartilage thickness changes over 1 year using 3 Tesla MRI. Specifically, we tested whether changes in central subregions exceed those in the total cartilage plates.

Methods: The right knees of a subsample of the OAI progression subcohort ($n = 156$, age 60.9 ± 9.9 years) were studied. Fifty-four participants had definite radiographic osteoarthritis (OA) (KLG 2 or 3) and a BMI > 30. Mean and minimal cartilage thickness were determined in subregions of the medial/lateral tibia (MT/LT), and of the medial/lateral weight-bearing femoral condyle (cMF/cLF), after paired (baseline, follow up) segmentation of coronal FLASHwe images with blinding to the order of acquisition.

Results: The central aspect of cMF displayed a 5.8%/2.8% change in mean thickness in the group of 54/156 participants, respectively, with a standardized response mean (SRM) of −0.47/−0.31, whereas cartilage loss in the total cMF was 4.1%/1.9% (SRM −0.49/−0.30). In the central MT, the rate of change was −1.6%/−0.9% and the SRM −0.29/−0.20, whereas for the entire MT the rate was −1.0%/−0.5% and the SRM −0.21/−0.12. Minimal thickness displayed greater rates of change, but lower SRMs than mean thickness.

Conclusions: This study shows that the rate of cartilage loss is greater in central subregions than in entire FT cartilage plates. The sensitivity to change in central subregions was higher than for the total cartilage plate in the MT and was similar to the total plate in the medial weight-bearing femur.

Key words: Cartilage, Magnetic resonance imaging, Osteoarthritis, Knee, Osteoarthritis Initiative.

Introduction

Magnetic resonance imaging (MRI) provides the opportunity to measure articular cartilage loss and other structural changes in knee osteoarthritis (OA) directly and three-dimensionally, whereas radiography is limited to the analysis of projections of the bone contours (i.e., joint space narrowing). MRI not only circumvents the challenges in appropriate positioning of the knee vs a two-dimensional film, but also permits one to acquire more comprehensive information on cartilage loss by providing specific information on each of the contacting cartilage plates in the femorotibial (FT) joint. Moreover, cartilage loss can be measured in subregions (i.e., central, internal, external) of FT cartilage plates[1–3], so one can gain additional insight into the spatial distribution of tissue loss throughout the cartilage plates in OA. Assuming that cartilage is not lost homogeneously throughout the plates, this approach may be used to identify subregions with a higher rate and sensitivity to change, which may, in turn, permit reductions in sample size in clinical studies for demonstrating, for instance, structure modifying effects of pharmaceutical compounds on disease progression.

We have recently presented a technique by which tibial cartilage can be reliably divided into central, internal, external, anterior, and posterior subregions, and the weight-bearing part of the femoral condyles into central, internal and external subregions, based on segmentation of the total subchondral bone area[3] (tAB). In a recent study by another group[2], the highest rates of change (% cartilage loss) were found in the central regions of the FT cartilages at 1.5 Tesla (T). However, these subregions appeared to have no advantage in terms of sensitivity for detecting change due to a proportional increase in the variability of change.

Division of cartilage plates into subregions has the additional advantage that the minimal cartilage thickness can

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be measured in central areas, whereas for total cartilage plates the minimal cartilage thickness always drops off towards zero towards the joint margins. Analogous to radiography, where minimal joint space width is considered a gold standard for measuring disease progression[4], regionalization has the advantage that the minimal cartilage thickness can be monitored three-dimensionally in the central joint areas. In a diseased joint, the minimal cartilage thickness may potentially be more sensitive to change than the mean thickness, because in central areas it is likely located at the site of a lesion, where cartilage loss may occur faster than in other parts of the joint surface.

Here we investigated whether subregional analysis of FT cartilage with 3 T MRI, testing central subregions of different sizes[3] as well as mean and minimal cartilage thickness[3], specific areas/parameters can be identified that provide a higher sensitivity to cartilage loss over time than the analysis of entire FT cartilage plates[5]. Specifically, we tested the hypothesis that changes in central subregions of the FT cartilages exceed those in total cartilage plates.

Methods

An age and gender stratified subsample of the Osteoarthritis Initiative (OAI) progression subcohort was studied (OAI public-use datasets 0.1.1, 0.B.1 and 1.B.1)[5], for which baseline and 1 year follow up MRI data were available. The subsample included 79 women with a mean (±standard deviation, SD) age of 60.3 ± 9.5 years (BMI = 30.3 ± 5.5) and 77 men, aged 62.0 ± 10.2 years (BMI = 30.1 ± 3.7). Participants were aged 45–79 years; 79 participants displayed a BMI of >30. The participants all had frequent knee symptoms (pain, aching or stiffness on most days of a month in past year) and radiographic OA (definite osteophytes in the postero-anterior [pa] fixed flexion radiographs[6,7]) in at least one knee in the initial readings of the baseline radiographs at the imaging sites. The baseline radiographs were acquired at the same time as the baseline MRIs. In a separate assessment, the baseline radiographs were then read independently by two readers (one musculoskeletal radiologist and one rheumatologist) at Boston University for Kellgren–Lawrence (K–L) grade. When there was a discrepancy in OA status by K–L grade (0–1 vs ≥ 2), readings were adjudicated by consensus with a third reader present. The results of these adjudicated reading were used in the present analysis. No data on knee alignment was available for this cohort.

The MRI sequence used to quantify cartilage morphology (see below) was only available in the right knees, whereas some participants displayed symptomatic and radiographic OA in their left knee. Further the adjudicated central radiographic readings differed slightly from the initial screening readings at the sites. Therefore, not all knees analyzed displayed radiographic knee OA. Of the 156 knees analyzed, 17 showed K–L grade = 0, 29 grade 1, 56 grade 2, 47 grade 3 and 7 grade 4. BMI has been identified as a risk factor for OA progression[2,8,9] and in a previous analysis of total cartilage plate changes in this cohort we found a trend for subjects with K–L grade 2 and 3 and high BMI to display greater cartilage thinning over 1 year than in those with low BMI and other K–L grades[5]. Also, clinical trials often include subjects with high BMI and definite radiographic OA, but not with end stage radiographic OA (K–L grade = 4), because there is little cartilage left to loose in the latter. For this reason, we additionally analyzed regional cartilage change in a "high risk" subcohort with K–L grade 2 or 3 radiographic OA and a BMI > 30 ($n = 54$).

Double oblique coronal 3D fast low angle shot (FLASH) MR images with water excitation (we), a slice thickness of 1.5 mm and an in plane resolution of 0.31 mm × 0.31 mm of the right knees were obtained at baseline and at year one follow up using 3 T MR scanners (Siemens Magnetom Trio, Erlangen, Germany) and a quadrature transmit-receive knee coils (USA Instruments, Aurora, OH). For further technical details on this imaging please see previous publications[5,10–12]. The reason for analyzing the FLASH sequence in all right knees rather than any of the other sequences acquired as part of the OAI protocol was that previously published reports on the rate and sensitivity to change of cartilage morphology have been based on the FLASH or similar sequences from other vendors.

All MR acquisitions were reviewed for artifacts, coverage and completeness by the MR technologists and were immediately reacquired if needed. Images were then sent for central archiving and preparation for release at Synarc Inc. and the UCSF Coordinating Center. A small sample of the MR images underwent visual quality assurance checks at Synarc and at UCSF. The MR images were provided on an external hard drive by the OAI Coordinating Center and were each quality controlled in detail and converted to a proprietary format at the image analysis center (Chondrometrics GmbH, Ainring, Germany). Segmentation of the FT cartilage plates was performed by seven technicians with formal training and at least 3 years of experience in cartilage segmentation[5]. Images were read in pairs blinded to the acquisition order. Segmentation included manual tracing of the tAB and the cartilage joint surface area (AC) of the medial tibia (MT), the lateral tibia (LT), the central (weight-bearing) medial femoral condyle (cMF) and the central lateral femoral condyle (cLF)[5,13]. The weight-bearing region of the femoral condyles was analyzed between the intercondylar notch and 60% of the distance to the posterior end of the femoral condyles[5,10,11]. Quality control of all segmentations was performed by a single expert (S.M.), reviewing all segmented slices of every data set[5]. The segmentations were used to compute the cartilage thickness over the entire subchondral bone area (ThCtAB) and included denuded areas as 0 mm cartilage thickness[5,13].

In MT and LT five subregions (central, internal, external, anterior, posterior) were computed based on the tAB (Fig. 1), with the central subregion initially (default) occupying 20% of the total tAB[3]. The central tibial region was defined as a cylinder around the center of gravity of the tibial tAB, in which the diameters were adapted to the individual shape of the bone interface area[3] (Fig. 1). Further computations were then performed with the central tibial region occupying 10%, 30%, 40% or 50% of the tibial tAB[3] (Fig. 2).

Since the weight-bearing femoral condyles are already limited in their anterior-posterior extension (by the femoral trochlea anteriorly, and the posterior femoral condyle posteriorly), they were subdivided into central, internal, and external strip-like regions of interest, each occupying 33.3% of the tAB in the initial (default) approach (Fig. 1). Further computations were then performed with the central femoral region occupying 25%, 50%, 66% and 75% of the femoral tAB[3] (Fig. 2).

The mean cartilage thickness was computed for all subregions, and the minimal cartilage thickness for the central subregions. Note that the minimal thickness was not determined at a single point, but was the mean of 1% of the smallest values in the central area[3]. The mean change from baseline to follow up, the SD of change, the standardized response mean (SRM = mean change/SD of change), and the significance of change (paired *t* test, without correction for multiple testing) was then calculated for each

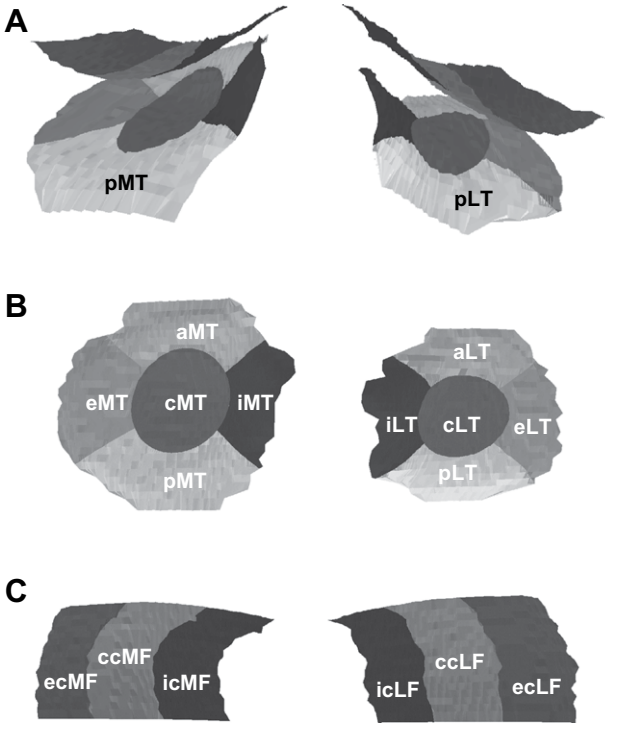

Fig. 1. Image showing the standard (default) FT subregions, with cMT covering 20% of the tibial subchondral bone area and ccMF covering 33% of the femoral subchondral bone area, respectively: (A) Posterior view of FT subchondral bone areas (tibia at the bottom, weight-bearing femur at the top), with subregions displayed by different gray values. (B) Superior view of the tibial subchondral bone area, with subregions labeled. (C) Inferior view of the femoral subchondral bone area, with subregions labeled cMF = central (weight-bearing) medial femoral condyle, ccMF = central cMF, ecMF = external cMF, icMF = internal cMF, MT = medial tibia, cMT = central MT, eMT = external MT, iMT = internal MT, aMT = anterior MT, pMT = posterior MT.