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Role of physical activity in cartilage damage progression of subjects with baseline full-thickness cartilage defects in medial tibiofemoral compartment: data from the Osteoarthritis Initiative

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SUMMARY

Objective: To assess the association between physical activity and cartilage damage progression in medial tibiofemoral compartment (MTFC) using 2-year follow-up magnetic resonance imaging (MRI) in subjects with denuded areas of subchondral bone (dABs) at the central weight-bearing medial femur (cMF) at baseline MRI examination.

Methods: One hundred subjects from the Osteoarthritis Initiative (OAI) progression cohort with dABs at the cMF at 3T MRI at baseline (51% men; mean age 62.2 years, range 45–79) were included. Sagittal 3D dual-echo steady-state with water excitation images were used to assess 2-year MTFC cartilage change. Associations between 2-year average Physical Activity Scale for the Elderly (PASE) and 2-year MTFC cartilage change were assessed by linear regression analysis. Subgroup analyses were performed.

Results: No associations between PASE and 2-year MTFC cartilage change were observed in the entire cohort. Similarly, in the subgroup with cartilage loss during the 2 years, the non-refuted confidence intervals for the regression coefficients were tightly clustered around the null value (regression coefficients for: mean cMF.ThCtAB = −0.00059; 98.75% CI: −0.00130 to 0.00012), cMF.dAB% = 0.02176; 98.75% CI: −0.02514 to 0.06865, Mean MT.ThCtAB = −0.00013; 98.75% CI: −0.00064 to 0.00038, MT.dAB % = 0.02543; 98.75% CI: −0.01485 to 0.06571.

Conclusion: In the entire group of subjects with dABs at the cMF at baseline, no association between physical activity and 2-year MTFC cartilage change was detected. Due to the limited sample size of our study, small-sized effects may not have been detected in our study.

Introduction

Knee osteoarthritis (OA) is one of the global leading causes of disability in the elderly population[1]. The lifetime risk of symptomatic knee OA is approximately 45%[2]. At present, there is no reliable treatment for regenerating cartilage in end stage OA and knee replacement (KR) is the final option for such patients[3]. While KR is a well-established choice for older patients, it can impose on daily activities. A recent study showed that about one third of patients have high level of residual symptoms following KR[4]. Current non-surgical options are aimed at relieving symptoms, increasing joint functionality, and slowing down progression of structural joint damage[5].

Advanced imaging modalities such as magnetic resonance imaging (MRI) have increasingly improved the diagnosis and risk stratification of patients with knee OA[6]. Denuded areas of subchondral bone (dABs) diagnosed using MRI can occur even at the early radiographic stages of knee OA[7] and they increase in size with worsening of disease severity[7]. Using MRI-based scoring systems, dABs in the medial tibiofemoral compartment (MTFC),

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especially at the central weight-bearing medial femur (cMF), demonstrate the highest hazard ratio for KR[8,9]. Of note, dABs in the lateral tibiofemoral compartment are not significantly associated with KR[8]. Therefore, subjects with dABs at the cMF, in particular, may benefit from therapies and risk-factor modifications that prevent further joint degeneration in order to delay KR. Although land-based physical activity can decrease pain and improve physical function in short-term[10], it is unclear whether it is beneficial or detrimental for the remaining cartilage in subjects who already have dABs at baseline MRI examination. In patients with predominantly MTFC OA in whom the knee was "unloaded"[11] by joint distraction for 2 months, a decrease in dABs and cartilage repair have been observed by MRI, with clinical improvement, sustaining for up to 2 years[12,13]. Conversely, it has also been shown that higher levels of physical activity are associated with greater risk for cartilage and other structural damages of the knee joint[14]. Therefore, we hypothesized that higher levels of physical activity are associated with a higher rate of cartilage loss in knees which already have dABs at the cMF at MRI at baseline. Thus, the purpose of the present study was to assess the association between physical activity and cartilage damage progression in MTFC using 2-year follow-up MRI in subjects with dABs at the cMF detected at baseline MRI examination. In line with previous work[8,11,12], as referred to above, we chose to limit our analyses to the MTFC. The lateral tibiofemoral compartment and the patellofemoral joint were not analyzed.

Methods

Patient selection

Data used in the preparation of this article were obtained from the online, publicly available database of the Osteoarthritis Initiative (OAI), a multi-center, longitudinal, prospective observational study of knee OA[15]. Four hundred and eighty-one subjects who had undergone quantitative assessments of MR images in project 9A[14] were eligible for inclusion. The subjects from project 9A formed the Core Image Assessment sample of the OAI progression sub-cohort, which was designed to provide longitudinal structural outcomes based on central image assessments[15]. By virtue of being in the OAI progression cohort, all subjects had symptomatic OA in at least one knee at baseline, which was defined as the combination of definite osteophytes (Kellgren and Lawrence [KL] grade $\geq$2)[16], based on the OAI clinical center screening reading and pain, aching or stiffness in or around the same knee on most days for at least 1 month during the past 12 months[15]. As part of the Core Image Assessment sub-cohort, a fixed-flexion knee radiograph and multisequence knee MRIs (including coronal intermediate-weighted turbo spin echo, sagittal intermediate-weighted turbo spin echo with fat-suppression, sagittal 3D dual-echo steady-state with water excitation [3D DESS WE], axial and coronal multiplanar reconstruction acquisitions) were available at baseline and 2-year follow-up[15].

Analysis plan

Our study was based on an exploratory observational investigation of the effect of physical activity (for which, PASE is a well-known surrogate) on the progression of knee OA (for which, the progression sub-cohort of the OAI cohort and the project 9A, have been a well-known focus of previous studies[17,18]) among subjects with established articular cartilage defects. Thus, choosing a targeted study population and selecting an appropriate definition of established articular cartilage defect was the main struggle of our plan. Since the definition of established articular cartilage defect could alter the sample size of our study, we conducted a power analysis prior to designing our final study. Power analysis indicated that small-sized (Cohen's f2 of 0.02), medium-sized (Cohen's f2 of 0.15) and large-sized (Cohen's f2 of 0.35) effects with an alpha of 0.05 and a power of 0.8 could be detected by investigating 684, 97, and 46 knees respectively[19]. Only 481 subjects had quantitative MR assessments of cartilage performed in the project 9A. Thus, as a limitation, our available samples were not large enough to justify the design of a study with the power to detect small-sized effect measures. Next, we chose a robust definition for established articular cartilage defect: presence of full-thickness defects in quantitative MR assessments of cartilage. Previous studies have highlighted the presence of full-thickness cartilage defects as one of the most important predictors of OA progression[9,20]. Subjects without dABs (dABs = 0%, with no full-thickness cartilage defect) at the cMF at sagittal 3D DESS WE scans at baseline ($n = 380$) and subjects in whom the physical activity scale for the elderly (PASE) at baseline was not available ($n = 1$), were excluded from the analysis. One hundred knees with dABs at the cMF at baseline of 100 subjects (51% men; mean age 62.2 years, range 45–79) were available for the final analysis (Fig. 1). This number was close to our a priori estimated sample size necessary for the detection of medium to large-size effect measures. Accordingly, four variables were selected as the outcomes of interest including changes in mean cartilage thickness and full-thickness cartilage defects in the cMF and MT areas, respectively. To account for multiple ($n = 4$) comparisons, a Bonferroni correction was also applied, dividing the *P*-value of significance by 4 ($P < 0.0125$). All confidence intervals were calculated to reflect the 98.75% confidence interval range. Likewise, we focused our discussion on the non-refuted states (values fitting within the 98.75% confidence intervals)[21].

Mean Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) physical function score[22] of the investigated knees at baseline was 17.6 (range 0–49). At baseline, all subjects had ipsilateral knee pain most days of a month in the past 12 months. Fifty-two subjects had a history of substantial ipsilateral knee injury, i.e., any history of ipsilateral knee injury sufficient to limit the ability to walk for at least 2 days, including during the 2-year follow-up. There were no ipsilateral knees undergoing KR during the 2-year follow-up period.

Assessment of physical activity

The PASE, a brief, easily scored, reliable and valid instrument for the assessment of physical activity in epidemiologic studies of

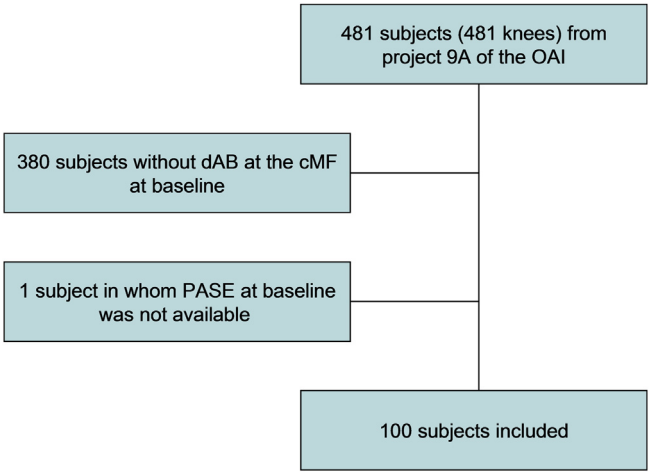

Fig. 1. Flowchart of the selection process and patient inclusion.