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Progression of cartilage degeneration and clinical symptoms in obese and overweight individuals is dependent on the amount of weight loss: 48-month data from the Osteoarthritis Initiative

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SUMMARY

Objective: To investigate compositional cartilage changes measured with 3T MRI-based T2 values over 48 months in overweight and obese individuals with different degrees of weight loss (WL) and to study whether WL slows knee cartilage degeneration and symptom worsening.
Design: We studied participants from the Osteoarthritis Initiative (OAI) with risk factors or radiographic evidence of mild to moderate knee OA with a baseline BMI ≥25 kg/m^2. We selected subjects who over 48 months lost a, moderate (BMI change, 5–10%, $n = 180$) or large amount of weight (≥10%, $n = 78$) and frequency-matched these to individuals with stable weight relative to their baseline BMI (<3%, $n = 258$). T2 maps of the cartilage compartments of the right knee, grey-level co-occurrence matrix (GLCM) texture and laminar analyses were evaluated and associations with WL and clinical symptoms (WOMAC subscales for pain, stiffness and disability) were assessed using multivariable regression models adjusting for age, sex, baseline BMI and KL.
Results: The amount of weight change was significantly associated with change in cartilage T2 of the medial tibia (β 0.9 ms, 95% CI 0.4 to 1.1, $P = 0.001$). An increase of T2 in the medial tibia was significantly associated with an increase in WOMAC pain (β 0.5 ms, 95% CI 0.2 to 0.6, $P = 0.02$) and disability (β 0.03 ms, 95% CI 0.003 to 0.05, $P = 0.03$). GLCM contrast and variance over all compartments showed significantly less progression in the >10% weight loss group compared to the stable weight group (SWG) (both comparisons, $P = 0.04$).
Conclusions: WL over 48 months is associated with slowed knee cartilage degeneration and improved knee symptoms.

Introduction

Obesity is a highly prevalent condition and is a major risk factor for knee OA[1,2]. Biomechanical factors such as increased joint loads and systemic metabolic factors have a negative impact on cartilage degradation[3–5]. Co-occurrence of these factors with obesity accelerates the cartilage degeneration process and worsens clinical symptoms[6,7]. Cartilage degeneration is associated with altered content of proteoglycans and water and degradation of the fibrillar collagen network[8]. Ideally, these findings should be diagnosed at early stages, before irreversible hyaline cartilage damage occurs. MRI-based T2 relaxation time has been identified as an imaging biomarker that provides information on early changes in collagen integrity[9]. Moreover, previous studies have shown that T2 measurements are able to predict changes in cartilage morphology and radiographic OA[10–12].

Studies demonstrated improvement of clinical performance through weight loss (WL)[13,14]. A previous study has shown that T2 relaxation times progress less in subjects with >10% WL of their baseline BMI over 4 years indicating decreased degenerative changes in comparison to controls without WL[15]. However,

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associations between T2 values in patients loosing weight over time and clinical parameters are not well understood. Another previous study found that percentage weight change was significantly associated with change in medial tibial cartilage volume[16], yet this study was limited to investigating cartilage volume only, without compositional imaging, which provides information on early changes in cartilage, even before cartilage volume loss may have taken place[9].

Previous studies have shown that quantitative analysis of cartilage texture using grey-level co-occurrence matrix (GLCM) texture parameters contrast, entropy and variance, allows early detection of compositional and structural changes within the cartilage matrix in subjects with risk for osteoarthritis, before radiographic evidence for OA is present, by providing information on the distribution of T2 pixel values[17,18]. Imaging of homogeneity may visualize early laminar disruption within cartilage, as does laminar analysis, which analyzes the bone and surface layer of cartilage separately[19].

Therefore, in this longitudinal study over 48 months in overweight and obese subjects we analyzed the association of different degrees of WL with changes in symptoms and change in cartilage T2, laminar and GLCM texture analysis parameters as measures of progression of knee cartilage degeneration.

Method

Subjects

The Osteoarthritis Initiative (OAI; http://www.oai.ucsf.edu) is an ongoing, longitudinal, prospective, multi-center cohort study with 4796 participants of which subjects for this study were selected. The initiative is sponsored by the U.S. National Institutes of Health (NIH) for investigation of diagnosis, treatment and prevention of OA. Subjects between 45 and 79 years of age with (progression cohort) or are at risk for (incidence cohort) symptomatic knee OA were included into this study. Knee imaging and clinical data were been obtained annually. Informed consent was obtained from all subjects and the study was HIPAA compliant. Study protocols, amendments and informed consent documentations were approved by the local institutional review boards. The following OAI datasets were used: baseline imaging dataset 0.E.1, 48 month follow-up imaging dataset 6.E.1, clinical datasets at baseline 0.2.2, 12 month follow-up 1.2.1, 24 month follow-up 3.2.1 and 48 month follow-up 6.2.2.

For our study, subjects with BMI for baseline, 12, 24, 36 and 48-month follow up were selected from the OAI database (progression and incidence cohort). Subsequently, subjects with missing BMI data at any of the four time points, a baseline Kellgren–Lawrence (KL) score > 3 in the right knee, or rheumatoid arthritis diagnosed during follow-up were excluded from these subjects. Of those, patients with an initial BMI of less than 25 kg/m^2 and a WL of 3–5% were excluded.

Since the trajectory of WL may affect longitudinal changes in joint structures and clinical symptoms, a linear regression model was implemented to assess the annual rate of change in BMI over 4 years. Weight change of the subjects was categorized into “steady” weight and “uneven” weight change, based on the root mean square error (RMSE) of the individual's regression line. In this study, we excluded subjects ($n = 84$) with uneven WL from the overall cohort, which was defined as an RMSE for weight change above the 95th percentile of the RMSE. Reason for this selection criteria was to select patients that follow the linear and steady WL trajectory in order to avoid a bias through subjects that “cycle” through weight gain and WL periods over 48 months and therefore to isolate the effects of continuous steady WL on knee cartilage as good as possible. Also subjects with development of cardiac failure, cancer and/or other severe diseases over the course of the 48-month study period, which could have been responsible for the WL, were excluded using the Katz comorbidity questionnaire[20]. From these subjects only those with right knee MRI T2 mapping sequences available at baseline and 48 months were selected. All subjects that were left after the previous mentioned exclusion criteria ($n = 1981$) were categorized into groups based on their WL over 48 months: moderate (BMI decrease of 5–10%), large amount (BMI decrease of >10%) of WL and stable weight (BMI changes <3%). We randomly selected subjects from among those in the 5–10% weight loss group (5–10%WLG; $n = 180$) and the >10% weight loss group (>10%WLG; $n = 78$) and frequency matched these on sex (m/f), age (10 year strata from 45 to 65 and one 14 year stratum from 65 to 79), baseline BMI (BMI in 2.5 kg/m^2 strata) and KL (KL in strata of 0/1 and 2/3). Subjects with stable weight ($n = 258$) were randomly selected from each stratum in the frequency matching process and matched to the respective WL subjects. This study design was chosen in order to minimize the impact of these covariates (age, sex, baseline BMI and KL) since their impact on the rate of T2 progression is known from previous studies[21–25].

The subject selection process is illustrated in Fig. 1 and subject characteristics are shown in Table I.

An a priori power analysis was performed to calculate the appropriate size of each subgroup in order to analyze differences between the groups. Using preliminary data of our previous study in controls ($n = 65$) and subjects with >10%WL ($n = 62$) over 48 months, the average change of T2 in the medial femur was 1.89 ± 1.98 ms in the control group and 0.67 ± 2.05 ms in the >10% WLG. With these data a comparison between two different WLGs was simulated and we determined a sample size of at least 70 subjects per group would achieve a power >0.9. Therefore we included 78 subjects in the >10%WLG and 180 subjects in the 5–10%WLG in order to ensure adequate group sizes for the comparison.

MR imaging

MR images were acquired using four identical 3.0T scanners (Siemens Magnetom Trio; Siemens Healthcare, Erlangen, Germany) and quadrature transmit-receive coils (USA Instruments, Aurora, OH, USA) at four sites (University of Maryland, School of Medicine, Baltimore, MD; University of Pittsburgh, Pittsburgh, PA; Memorial Hospital of Rhode Island, Pawtucket, RI and The Ohio State University, Columbus, OH). T2 values were obtained using sagittal two-dimensional multislice, multiecho sequences with seven echo times (TEs 10 ms, 20 ms, 30 ms, 40 ms, 50 ms, 60 ms, and 70 ms). Further details are available in the OAI MR protocol[26].

Image analysis

Semi-automatic cartilage segmentation of lateral femur, lateral tibia, medial femur, medial tibia and patella compartments was performed as previously described, using an in-house, spline-based software based on MATLAB (MathWorks, Natick, Massachusetts). This algorithm also calculated the mean cartilage thickness of all ROIs for each compartment as previously described[12]. Cartilage was segmented and graded by two trained researchers (M.S. and G.F.), applying this semi-automatic cartilage segmentation tool using the first echo of the MSME sequence and manually correcting the position of control points if needed, in consensus, and under supervision of an experienced radiologist (T.M.L.).

Only artifact-free slices with well-defined boundaries of cartilage were segmented. The trochlea was not segmented because of interfering flow artifacts from the popliteal artery. For each

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