Osteoarthritis and Cartilage 22 (2014) 226–234

Osteoarthritis and Cartilage

OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

Quadriceps intramuscular fat fraction rather than muscle size is associated with knee osteoarthritis

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ARTICLE INFO

Article history:
Received 30 August 2013
Accepted 2 December 2013

Keywords:
Quadriceps strength
Water/fat imaging
Hamstrings
Cartilage

SUMMARY

Objectives: To compare thigh muscle intramuscular fat (intraMF) fractions and area between people with and without knee radiographic osteoarthritis (ROA); and to evaluate the relationships of quadriceps adiposity and area with strength, function and knee magnetic resonance imaging (MRI) lesions.
Methods: Ninety six subjects (ROA: Kellgren–Lawrence (KL) > 1; $n = 30$, control: KL = 0, 1; $n = 66$) underwent 3-T MRI of the thigh muscles using chemical shift-based water/fat MRI (fat fractions) and the knee (clinical grading). Subjects were assessed for isometric/isokinetic quadriceps/hamstrings strength, function Knee injury and Osteoarthritis Outcome Score (KOOS), stair climbing test (SCT), and 6-minute walk test (6MWT). Thigh muscle intraMF fractions, muscle area and strength, and function were compared between controls and ROA subjects, adjusting for age. Relationships between measures of muscle fat/area with strength, function, KL and lesion scores were assessed using regression and correlational analyses.
Results: The ROA group had worse KOOS scores but SCT and 6MWT were not different. The ROA group had greater quadriceps intraMF fraction but not for other muscles. Quadriceps strength was lower in ROA group but the area was not different. Quadriceps intraMF fraction but not area predicted self-reported disability. Aging, worse KL, and cartilage and meniscus lesions were associated with higher quadriceps intraMF fraction.
Conclusion: Quadriceps intraMF is higher in people with knee OA and is related to symptomatic and structural severity of knee OA, whereas the quadriceps area is not. Quadriceps fat fraction from chemical shift-based water/fat MR imaging may have utility as a marker of structural and symptomatic severity of knee OA disease process.

Introduction

Considerable research has focused on the characterization of morphological and compositional changes in cartilage and bone in knee osteoarthritis (OA)[1]. However, little attention has been paid to the quantification of adipose tissue at the thigh despite the strong relationship between obesity and knee OA[2]. Greater thigh adiposity is known to be associated with lower strength, worse mobility, and worse lipoprotein profiles in older adults[3–5]. Lower leg lean mass has been shown to be related to a greater risk of incident knee radiographic OA (ROA)[6]. Using computed tomography (CT), Conroy *et al.* found that people with ROA had greater whole body lean and muscle tissue, greater quadriceps cross-sectional area and lower quadriceps specific torque (torque per unit muscle area)[7]. Using T_1-weighted magnetic resonance (MR) images from the Osteoarthritis Initiative (OAI) datasets, women with ROA were found to have greater intermuscular fat volume; and greater intermuscular fat volume had weak association with lower quadriceps strength and worse physical performance[8].

CT based techniques for quantifying muscle adiposity require exposure to ionizing radiation and the conventional T_1-weighted

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http://dx.doi.org/10.1016/j.joca.2013.12.005

MR imaging does not allow an accurate determination of intermuscular adipose tissue (IMAT) in localized regions[9,10]. In T_1-weighted images, the IMAT[11] includes the visible fat signal both within the muscles intramuscular fat (intraMF) and between the muscles (intermuscular fat). Chemical shift-based water/fat separation methods, including Dixon techniques[12,13] and the iterative decomposition of water and fat with echo asymmetry and least-squares estimation (IDEAL)[14], provide a valuable alternative approach for quantification of fatty infiltration. These techniques overcome the limitations of conventional T_1-weighted imaging by allowing high spatial resolution for quantification of adipose tissue in localized regions. Chemical shift-based water/fat separation techniques have been used for quantification of fat fractions at the liver[15], with very good agreement with MR spectroscopy[16]. Using this technique, we have earlier found individuals with diabetes to have greater intraMF in the calf muscles when compared with controls, but no difference in intermuscular fat[17]. Quantitative measures of intraMF were observed to correlate very well with established semi-quantitative grading of fatty infiltration at the calf and the shoulder[18,19].

In people with knee OA, quadriceps weakness is a ubiquitous clinical finding[20]. Loss of muscle tissue only partly explains the loss of strength in people with OA[7,20] and fatty infiltration of thigh skeletal muscle is known to affect muscle strength and mobility in the elderly[3,4]. However, quantitative MR imaging techniques have so far not been used to assess intraMF of quadriceps in people with knee OA. Also, metrics of morphologic and compositional changes in knee cartilage, meniscus and bone with knee OA have not shown strong relationships with patient symptoms and functional outcomes[21]. If quantitative measures of quadriceps adiposity are related to patient symptoms and function, these measures may be used as determinants of the OA disease process. Hence, the aims of this study were (1) to quantify intraMF and area of the quadriceps and other thigh muscles in individuals with and without ROA, and (2) to investigate the relationships between quadriceps fat fractions, muscle area, muscle strength, function and structural severity of knee OA.

Patients and methods

Subjects

Subjects were recruited from the community as a part of a larger study on knee OA. The inclusion criteria for OA patients were age > 35 years, frequent clinical symptoms of OA and radiographic signs of OA[22]. The controls were older than 35 years and without history of diagnosed OA, clinical OA symptoms, previous knee injuries, or signs of OA on radiographs. Standing radiographs using the fixed-flexion protocol[23] using a synaflexor device were obtained for all subjects to determine the Kellgren–Lawrence (KL) grade[24]. The 96 subjects (43 men, 53 women) participated in this cross-sectional study. Of these, 66 were classified as controls (KL = 0, 1), and 30 were classified as having ROA (KL score > 1). All subjects signed a written informed consent prior to participation in the study and all protocols were approved by a University of California, San Francisco (UCSF) Committee on Human Research.

Magnetic resonance imaging (MRI) acquisition

MRI was performed using a 3-T GE Signa HDx MR Scanner (General Electric, Milwaukee, WI, USA) and an eight-channel transmit-receive knee coil (Invivo, Orlando, FL, USA). For the ROA subjects, the knee with more severe findings on the radiographs was imaged. In controls, the extremity was selected at random. For clinical grading, a high resolution 3-D T_2-weighted fast spin echo sequence (Repetition Time [TR]/Echo Time [TE] = 1500/26.69 ms, matrix = 384 × 384, slice thickness = 0.5 mm, echo train length = 32, bandwidth = 37.5 kHz, NEX = 0.5, acquisition time = 10 min 30 s) was used. For assessment of thigh adiposity and muscle cross-sectional area, the imaging was performed over a volume 14 cm (28 slices) proximal to the superior pole of the patella. Axial 2-D T_1-weighted images (TR/TE = 600/5.52 ms, matrix = 384 × 192, slice thickness = 5 mm, echo train length = 7, bandwidth = 93.75 kHz, NEX = 2.0, acquisition time = 1 min 56 s) were acquired for segmentation of thigh muscles. An investigational version of the chemical shift-based water-fat separation method known as IDEAL[14], implemented in a multi-shot multi-echo 3D spoiled-gradient echo (SPGR) acquisition[25] (TR/TE = 11/1.31 ms, acquisition matrix = 180 × 180, slice thickness = 5 mm, Flip angle = 3, bandwidth = 58.59 kHz, acquisition time = 3 min 00 s), was used to measure fat content. The separation of water and fat signal was based on the IDEAL algorithm[14] with the multi-peak fat spectrum model and single T_2* correction[15]. In-phase images were calculated by taking the sum of the separated water and fat images. Out-of-phase images were also calculated by taking the absolute value to the difference of the separated water and fat images. Fat fraction images were generated by computing the ratio of the separated fat signal over the sum of the separated water and fat signals.

Semi-quantitative clinical grading of knee lesions

A modified-whole-organ magnetic resonance imaging score (mWORMS) UCSF classification has been introduced by our research group in which the number of the anatomical compartments is reduced to six (patella, trochlea, medial femur, lateral femur, medial tibial, lateral tibia)[26,27] from 15 in the original score[28]. In the WORMS scoring, higher scores reflect greater severity of the structural feature being reported. This classification system was used to assess severity of cartilage and meniscus and bone marrow lesions (BML), by board certified musculoskeletal radiologists (TML with 22 and LN with 6 years of experience). The radiologists were blinded to subject information and performed separate readings, with a consensus in case of disagreement. For each subject, the scores for all compartments (patella, trochlea, lateral/medial femur/tibia) were added to obtain a total score for each feature – cartilage, meniscus and BML.

Fat fraction and lean anatomical cross-sectional area (ACSA) quantification

All analyses were performed in a custom written Matlab (MathWorks, Natick, MA, USA) program. Individual muscle regions of interest (ROIs) for quadriceps (vastus medialis, vastus lateralis, vastus intermedius, rectus femoris), hamstrings (semimembranosus, semitendinosus, biceps femoris long head, biceps femoris short head), other muscle groups (adductor group, gracilis and sartorius) were manually segmented by a single trained researcher (WL) on the axial T_1-weighted images. The region of interest segmented consisted of four slices (2 cm section) between 10 and 12 cm proximal to superior pole of the patella. These segmentations were transferred to the fat fraction maps from the axial IDEAL images. For this study, the intraMF fraction, intraMF volume and lean ACSA variables were calculated for the quadriceps, hamstrings and other muscles compartments as well as for global (all muscles) compartment (Fig. 1). The lean ACSA for each muscle was the area of the muscle minus the area of the intraMF. The subcutaneous adipose tissue (SAT) and IMAT regions were segmented using an automatic algorithm published previously[29]. The intermuscular fat compartment consisted of the IMAT region outside of