Title

Association of Quadriceps Adiposity With an Increase in Knee Cartilage, Meniscus, or Bone Marrow Lesions Over Three Years

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Quadriceps adiposity is associated with increase in lesions of the knee cartilage, meniscus, or bone marrow over 3-years

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Abstract

Objective: To evaluate the association of fatty infiltration of the quadriceps and vastus medialis (VM) with increase in knee cartilage, meniscus, or bone marrow lesions (BML) from MRI in knee osteoarthritis (OA) over 3-years.

Methods: Participants (n=69) with and without radiographic knee OA underwent MRI at baseline and 3-years later. Chemical shift-based water/fat MRI were used to quantify the intramuscular fat fraction and the lean anatomical cross-sectional area (ACSA) for the VM and entire quadriceps muscles. MRI images of the knee were analyzed using semi-quantitative modified WORMS (mWORMS) grading to assess change in lesions in the articular cartilage, meniscus, and BML. Logistic regression was used to assess if baseline quadriceps and VM fat fraction and lean ACSA were associated with increase in mWORMS scores. Odds ratios (ORs) were adjusted for age, sex, and BMI.

Results: Overall 62% (43/69) of subjects had an increase in cartilage (26/43), meniscus (19/43), or BML (22/43) scores. Quadriceps (OR: 2.13 [95% confidence interval: 1.09, 4.15]) and VM (OR: 2.05 [95% confidence interval: 1.25, 3.36]) fat fraction were both associated with an increase in cartilage, meniscus, or BML scores over 3-years. The association of quadriceps or VM lean ACSA with the outcomes was not significant.

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Conclusions: These longitudinal findings using quantitative MRI methods for assessment of muscle adiposity highlight the role of quadriceps adiposity, specifically VM, in knee OA progression. However, studies in larger cohorts are needed to confirm these findings.

Keywords

muscle; fat; MRI; osteoarthritis; Dixon

INTRODUCTION

Intramuscular quadriceps adiposity is increasingly being recognized as an important component of the knee osteoarthritis (OA) pathogenesis (1-3). The mechanisms are likely related to release of inflammatory cytokines from the adipose tissue and their effects on the knee joint, as well as, effects of muscle adiposity on muscle function(4). Quadriceps adiposity might be responsive to exercise interventions(5), and hence, its effects on knee joint health and OA need to be determined. Chemical shift-based water/fat separation MRI techniques allow for quantification of intramuscular adipose tissue (i.e, fat stored within the muscle fibers) and show very good agreement with MR spectroscopy (6-8). These techniques provide higher spatial resolution for quantification of adiposity than is available from conventional T1-weighted MRI images (9).

Using quantitative and validated chemical shift-based water/fat MRI techniques, we previously observed that people with knee OA have increased intramuscular fat fraction in the quadriceps muscle compared to people without knee OA, even after adjusting for age, sex, and BMI (10). Fat fraction refers to the ratio of separated fat signal over the sum of separated water and fat signals from the chemical shift-based water/fat MRI. We also observed that intramuscular fat fraction of the quadriceps, and not lean anatomical cross sectional area (ACSA), was associated with clinical outcomes of knee OA (10). Other studies reported that fatty infiltration of vastus medialis (VM) might be implicated in changes in cartilage lesions and bone marrow lesions (BMLs) (2, 3). However, it is not known if quadriceps adiposity using chemical shift-based water/fat MRI is associated with longitudinal changes in knee OA.

Intramuscular adiposity of the quadriceps could lead to knee lesions that worsen over time leading to OA. Our objective was to assess if intramuscular fat fraction of the quadriceps (i.e., VM, vastus lateralis (VL), vastus intermedius (VI), and rectus femoris (RF)) is associated with increase in knee cartilage lesions, meniscus lesions, or BMLs over 3-years in adults with and without knee OA. Since prior studies have identified VM adiposity as being related to knee OA(2, 3), and since the chemical shift-based water/fat MRI allows for quantification of adiposity within the individual quadriceps muscles at high-resolution, the second objective was to assess if intramuscular fat fraction of VM is associated with increase in knee cartilage lesions, meniscus lesions, or BMLs over 3-years in adults with and without knee OA. As exploratory analyses, we also investigated the role of other individual quadriceps muscles, i.e., VL, VI, and RF, as this has not been studied previously.

METHODS

Participants:

Data for this study were collected as a part of a longitudinal observational study in individuals with and without knee OA. The study was conducted at an urban academic research Institution. Participants were recruited from the community using advertisements and flyers. The inclusion criteria for individuals with knee OA were age > 35 years, knee pain, aching, or stiffness on most days per month during the past year, or use of medication for knee pain on most days per month during the past year, and radiographic signs of OA. The inclusion criteria for controls were age > 35 years, no history of diagnosed OA or OA symptoms, previous knee injuries, or signs of OA on radiographs. The exclusion criteria were concurrent use of an investigational drug, history of intra-articular fracture or surgical intervention in the study knee, conditions other than OA which limit lower extremity function and mobility and/or would confound the evaluation of function, and contraindications to MRI. A musculoskeletal radiologist with over 22 years of experience (TML) determined radiographic OA using the Kellgren-Lawrence grade (KLG) from bilateral weight-bearing posterior anterior radiographs using the fixed-flexion protocol with a synaflexor device. Radiographic OA was defined as KLG≥2. All participants who had baseline muscle MRI measurements, and baseline and 3-year MRI measurements were included in these analyses. The Knee injury and Osteoarthritis Outcome Score (KOOS) pain subscale and stair climbing test were used to assess pain and physical function respectively. All subjects signed a written informed consent prior to participation; procedures were approved by the Institutional Committee on Human Research.

MR Imaging:

All participants underwent 3.0 Tesla MRI (GE Signa HDx, General Electric, Milwaukee, WI, USA) with an eight-channel transmit-receive knee coil (Invivo, Orlando, FL, USA). MRI sequences have been described previously (10). High resolution images were acquired for semi-quantitative scoring of knee OA. A modified- whole-organ magnetic resonance imaging score (mWORMS) was used to assess cartilage, meniscus, and bone marrow lesions (BML) by three experienced board certified musculoskeletal radiologists (11). Cartilage and BML were assessed over 6 subregions (medial and lateral femur, medial and lateral tibia, patella, and trochlea). Meniscus was assessed over 6 subregions (anterior horn, posterior horn, and body of medial and lateral menisci). We have previously reported high reproducibility (ICC of 0.98, 0.97, and 0.97 for cartilage, meniscus, and BML, respectively) for these measures(11, 12). The radiologists were blinded to subject information and performed separate readings with a consensus in case of disagreement. Paired readings were performed to assess longitudinal changes in MRI scores from baseline to 3-years. Individuals were categorized into those with and without an increase in cartilage, meniscus, or BML scores. The score at 3-years had to be >1 for cartilage or meniscus lesions to only identify subjects with morphological lesions rather than signal change.

Details of quantification of intramuscular fat fraction and lean ACSA have been published previously (10). All images were acquired from a volume 14 cm (28 slices) proximal to the superior pole of the patella. For muscle adiposity, an investigational version of the chemical

shift based water-fat separation (7), implemented in a multi-shot multi-echo 3D spoiled-gradient echo (SPGR) acquisition was used (13). The separation of water and fat signal was based on the iterative decomposition of water and fat with echo asymmetry and least-squares estimation (IDEAL) algorithm (7) with the multi-peak fat spectrum model and single T_2* correction (14). 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 of 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. Individual quadriceps muscles (VM, VL, VI, and RF), were segmented on 4 slices (2 cm region of interest between 10-12 cm proximal to superior pole of the patella) on axial T_1 weighted images by trained researchers in a custom written Matlab (Mathworks, Natick, MA, USA) program. These segmentations were transferred to the fat fraction maps from the IDEAL images. Intramuscular fat fraction (in %, fatty infiltration within an individual muscle) and Lean ACSA (in cm^2, area of the muscle minus the area of the intramuscular fat) were then calculated for each muscle (10). Average over the 4 slices for both of these measures was used in the analyses. We have previously reported the high reproducibility for intramuscular fat measurements (10).

Statistical analysis:

Logistic regression was used to evaluate the association of (1) baseline quadriceps intramuscular fat fraction and lean ACSA, and (2) baseline VM intramuscular fat fraction and lean ACSA, with an increase in MRI scores for lesions in cartilage or meniscus or BML. Effect measures for potential associations were expressed as odds ratios (ORs) and the corresponding confidence intervals. The analyses were adjusted for baseline age, sex, and BMI. A secondary set of regression models was developed to assess the associations of other intramuscular fat fraction and lean ACSA for VL, VI, and RF with increase in MRI scores. Reproducibility of KLG was assessed using a weighted Kappa statistic with quadratic weighting from a subset of 20 knees that were graded 2-weeks apart.

RESULTS

Of the 96 participants at baseline, 72% (69) returned for the 3-year visit. Baseline characteristics of the study participants are presented in Table 1. Compared to participants retained, the participants who were lost to follow-up were not statistically different in age (50.8±9.5 years; p=0.262) and BMI (24.7±3.9 kg/m^2; p=0.630), and distribution of sex (65% female; p=0.224), KLG (21% KLG>2; p=0.177), and presence of cartilage lesions, meniscus lesions, or BML at baseline (69% with lesions; p=0.513). Overall, 62% (43/69) of subjects had an increase in either cartilage (26/43), meniscus (19/43), or BML (22/43) scores over 3-years. Frequency of increase in each subregion as well as frequency of increase by number of subregions for cartilage, meniscus, and BML are shown in Table 2. Majority of the participants showed increase in < 4 subregions for each MRI feature. The Kappa statistic was 0.96 showing high reproducibility of the KL grading.

Results from the logistic regression analyses on the association of baseline VM fat fraction and lean ACSA with the study outcomes are presented in Table 3. Greater quadriceps and

VM intramuscular fat fraction were associated with a greater odds of increase in MRI scores over 3-years. Quadriceps and VM lean ACSA were not associated with the outcome of interest. Additionally, older age (both models) and female sex (VM model) were associated with greater odds of increase in MRI scores over 3-years. Overall, 28/36 females (78%) and 15/33 (45%) of males showed increase in lesions. VL, VI, or RF fat fraction were not found to be associated with an increase in MRI scores after adjustment (Supplementary table).

DISCUSSION

We found that an increase in the intramuscular fat fraction of the quadriceps, particularly VM, was associated with greater odds of MRI degeneration over 3-years in the knee. Our effect measures relied on a quantitative MRI measure of muscle adiposity that has been validated and has been shown to provide a more reliable assessment than alternative MRI or CT measures. Our results highlight the importance of muscle adiposity in the knee OA disease process and offer a potential target for therapeutic interventions. However, considering the attrition among participants and relatively small sample size, these findings should be confirmed in larger studies.

We observed that greater quadriceps and VM intramuscular fat fraction was associated with a greater risk of MRI degeneration of the knee over 3-years. In a study by Raynauld et al., that used data from a clinical trial in people with knee OA, it was shown that increase in VM intramuscular fat over 2-years was associated with worsening of cartilage loss and BML scores (2). In another study by Teichtahl et al. among healthy adults trying to lose weight and excluding people with diagnosed knee OA, a reduction in VM fat infiltration over 1.5 to 4 years was associated with a reduced annual loss of medial tibial and patella cartilage (3). Our results support these previous findings but there are important differences in the studies that should be noted. These previous studies used an MRI measure that has not been validated against established gold standard techniques like MR spectroscopy. We have used a measure of intramuscular adiposity that has been validated and used in multiple research studies including measurements of fat fraction in the liver (8). Raynauld et al. assessed concomitant changes in VM fat and cartilage and BML scores over 2-years. Hence, it is unclear whether increase in VM fat was a cause or consequence of worsening MRI OA. Teichtahl et al. excluded people with knee OA limiting interpretations about role of VM adiposity in people with knee OA. However, our study and these previous findings do suggest that therapies targeted at reducing fatty infiltration of thigh muscles needs to be explored in people with knee OA. For instance, increasing physical activity can increase lean muscle mass and decrease fatty infiltration of muscles (15). A recent clinical trial reported that periodized circuit training resulted in reductions in thigh intermuscular fat in people with knee OA when compared to strength training and education groups(5).

The mechanisms underlying the role of VM fat fraction in knee OA progression are not clear. An increase in intramuscular fat fraction and/or decrease in lean ACSA leads to weakness that could in theory reduce the stability of the knee during dynamic activities and cause abnormal loading. Quadriceps weakness has been shown to be a risk factor for knee OA progression (16). It is also possible that adipose tissue in the thigh muscles, that shares a direct vascular connection with the muscle it infiltrates, is associated with impaired fat

oxidation (17) and unfavorable lipoprotein profiles (18). Further research is needed to clarify the metabolic activity of the intramuscular fat depots of the VM in people with knee OA. It is also possible that VM is preferentially involved in knee OA. A recent study compared VM biopsy from patients with end-stage knee OA who underwent arthroplasty with patients without OA (19). The authors reported a significantly lower myofiber-occupied area and greater ectopic interstitial adipogenesis in the perimysium and endomysium of people with OA. Individuals with OA had 30.4% of VM area occupied with adipose tissue vs. 4% for people without OA. The authors did not evaluate other quadriceps muscles. Assuming a similar amount of fatty infiltration in all quadriceps muscles, it is possible that the VM is most affected earlier being the smallest of the uni-articular quadriceps muscles. However, it is also possible that the findings are related to our measurement of adiposity and lean ACSA. We used a region of interest consisting of a 2 cm section of the thigh 10-12 cm proximal to the superior pole of the patella. It is possible that our method captured fatty infiltration of VM more than the other quadriceps which are larger and extend significantly more in the proximal direction.

There are limitations of this study that should be considered. Our cohort consisted of community-dwelling active, and high functioning individuals. Hence, the results may not be generalizable to individuals with more advanced OA or greater functional limitations. We defined our outcome as increase in scores for either cartilage or meniscus or bone marrow. This does not allow for interpretations regarding associations of quadriceps adiposity and individual features of knee OA or individual subregions within the knee joint. Our study also included a relatively small sample and these results should be confirmed in larger cohorts.

In conclusion, we observed that greater fatty infiltration of the quadriceps muscle, and particularly the VM muscle, were related to increased risk of worsening knee OA assessed using MRI. These results suggest that quadriceps adiposity could be a target for therapeutic interventions. However, these findings need confirmation in larger cohorts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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SIGNIFICANCE AND INNOVATIONS

- Fatty infiltration of the quadriceps is implicated in pathogenesis of knee osteoarthritis (OA). However, prior studies have not used validated quantitative measures of muscle adiposity. Chemical shift-based water/fat MRI provide an objective and valid measurement of muscle adiposity.
- The results from this longitudinal study show that fatty infiltration of the quadriceps muscle, particularly the vastus medialis, is related to greater odds of increase in knee cartilage, meniscus, or bone marrow lesions over 3-years.
- The results also demonstrate that loss of quadriceps or vastus medialis anatomical cross-sectional area is not associated with increase in knee cartilage, meniscus, or bone marrow lesions over 3-years.
- These findings further highlight the role of changes in quadriceps muscle adiposity in knee OA and, if confirmed in larger cohorts, could be used to guide interventions.

Table 1.

Demographics, distribution of radiographic and MRI scores, and baseline muscle fat fraction and lean ACSA.

	Baseline Characteristics (n=69)
Age (years) *	53.3 (10.1)
Weight (kg) *	66.9 (9.7)
Height (m) *	1.7 (9.1)
BMI (kg/m^2) *	24.3 (3.25)
Females (n[%])	36 (55.2%)
KOOS Pain *	90.4 (13.0)
Stair Climbing Test (s) *	11.4 (1.9)
Had radiographic OA (n[%])	24 (34.8%)
KLG0 (n[%])	KLG0 = 27 (39.1%)
	KLG1 = 18 (26.1%)
	KLG2= 6 (8.7%)
	KLG3=15 (21.7%)
	KLG4=3 (4.3%)
Had Lesions in cartilage or meniscus or BML (n[%])	52 (75.4%)
Had Cartilage Lesion (mWORMS>1 in any compartment) (n[%])	44 (63.8%)
Had Meniscus Lesion (mWORMS>1 in any compartment) (n[%])	26 (37.7%)
Had BML (mWORMS >0 in any compartment) (n[%])	34 (49.3%)
Intramuscular Fat Fraction (%)	
Quadriceps *	5.2 (1.9)
Vastus Medialis *	7.0 (2.3)
Vastus Lateralis *	7.5 (2.7)
Vastus Intermedius *	6.8 (2.9)
Rectus Femoris *	9.0 (6.2)
Lean ACSA (cm^2)	
Quadriceps *	31.7 (7.8)
Vastus Medialis *	11.4 (3.5)
Vastus Lateralis *	9.5 (2.6)
Vastus Intermedius *	9.5 (2.6)
Rectus Femoris *	1.4 (0.7)

* Mean (standard deviation) reported

KOOS = Knee injury and Osteoarthritis Outcome Score; KLG = Kellgren-Lawrence Grade; BML = Bone Marrow Lesion; ACSA = Anatomical Cross-Sectional Area

Table 2.

Distribution of increase in MRI scores across subregions

Frequency of increase in each subregion				
Cartilage/BML Subregions	**Frequency of increase for cartilage lesions**	**Frequency of increase for BML**	**Meniscus subregion**	**Frequency of increase for meniscus lesions**
Medial Femur	6	3	*Medial Meniscus – anterior horn*	5
Medial Tibia	4	4	*Medial Meniscus - body*	7
Lateral Femur	3	5	*Medial Meniscus – posterior horn*	8
Lateral Tibia	4	4	*Lateral Meniscus – anterior horn*	4
Patella	18	8	*Lateral Meniscus - body*	4
Trochlea	3	7	*Lateral Meniscus – posterior horn*	5

Frequency of increase by number of subregions			
Number of subregions with increase	**Cartilage**	**BML**	**Meniscus**
1	19	15	11
2	3	5	3
3	3	2	4
4	1	0	0
5	0	0	1
6	0	0	0

BML = Bone Marrow Lesion

Table 3.

Results from logistic regression models for classification of participants into those with and without increase in MRI scores over 3-years.

Variable	Odds Ratio	95% Confidence Intervals
Model with quadriceps intramuscular fat fraction and lean ACSA		
Quadriceps Intramuscular Fat Fraction (%)	2.13	1.09, 4.15
Quadriceps Lean ACSA (cm)	1.07	0.96, 1.20
Age (years)	1.11	1.04, 1.19
Sex[*]	0.15	0.03, 0.76
BMI (kg/m^2)	0.93	0.72, 1.19
Model with VM intramuscular fat fraction and lean ACSA		
VM Intramuscular Fat Fraction (%)	2.05	1.25, 3.36
VM Lean ACSA (cm)	1.21	0.94, 1.55
Age (years)	1.13	1.04, 1.22
Sex[*]	0.17	0.03 , 0.91
BMI (kg/m^2)	0.88	0.68, 1.13

VM = vastus medialis; ACSA = Anatomical Cross-Sectional Area

For all variables except sex, odds ratios are per one unit increase in the exposure

[*] Reference group = females