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Thigh muscle composition changes in knee osteoarthritis patients during weight loss: Sex-specific analysis using data from osteoarthritis initiative

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Objectives: Sex of patients with knee osteoarthritis (KOA) may impact changes in thigh muscle composition during weight loss, the most well-known disease-modifying intervention. We investigated longitudinal sex-based changes in thigh muscle quality during weight loss in participants with KOA.
Methods: Using Osteoarthritis Initiative (OAI) cohort data, we included females and males with baseline radiographic KOA who experienced > 5 % reduction in Body Mass Index (BMI) over four years. Using a previously validated deep-learning algorithm, we measured Magnetic Resonance Imaging (MRI)-derived biomarkers of thigh muscles at baseline and year-4. Outcomes were the intra- and inter-muscular adipose tissue (Intra-MAT and Inter-MAT) and contractile percentage of thigh muscles between females and males. The analysis adjusted for potential confounders, such as demographics, risk factors, BMI change, physical activity, diet, and KOA status.
Results: A retrospective selection of available thigh MRIs from KOA participants who also had a 4-year weight loss (> 5 % of BMI) yielded a sample comprising 313 thighs (192 females and 121 males). Female and male participants exhibited a comparable degree of weight loss (females: −9.72 ± 4.38, males: −8.83 ± 3.64, P-value=0.060). However, the changes in thigh muscle quality were less beneficial for females compared to males, as shown by a less degree of longitudinal decrease in Intra-MAT (change difference,95 %CI: 783.44 mm^2/4-year, 505.70 to 1061.19, P-value < 0.001) and longitudinal increase in contractile percentage (change difference,95 %CI: −3.9 %/4-year, −6.5 to −1.4, P-value=0.019).
Conclusions: In participants with KOA and 4-year weight loss, the longitudinal changes in thigh muscle quality were overall beneficial but to a less degree in females compared to males. Further research is warranted to investigate the underlying mechanisms and develop sex-specific interventions to optimize muscle quality during weight loss.
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Introduction

Increased body fat mass and obesity are recognized as the main modifiable risk factors for the development and progression of knee osteoarthritis (KOA).[1,2] Obesity increases the risk of incident radiographic KOA with the relative risk of 2.29 for females and 1.73 for males.[3] Obesity triggers a chronic, systemic, low-grade inflammation[4] while the added biomechanical stress[5] caused by excess weight

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increases the likelihood of osteoarthritis (OA) development and progression. Additionally, the knee joint is surrounded by substantial fat tissue (subcutaneous fat, intramuscular fat, and infrapatellar fat) that releases pro-inflammatory mediators.[6,7] The inflammatory cytokines released by total body fat and local fat tissue around the knee contribute to the degeneration of articular tissue, leading to structural and clinical KOA.[4,8]

Given that obesity is a modifiable risk factor for KOA, weight loss is a recommended intervention to improve KOA outcomes.[9] A meta-analysis revealed that a 5 % weight loss is associated with moderate to substantial improvements in self-reported KOA symptoms.[10] Considering the potentially modifiable nature of thigh muscle through specific exercises and interventions,[11,12] it seems vital to maintain the quality of these muscles when suggesting weight loss for managing KOA. Recent evidence indicates that weight loss using a combination of high protein diet and resistance exercise may lead to a decrease in intermuscular adipose tissue and an increase in muscle mass.[13–15]

There is emerging evidence suggesting that changes in body composition due to weight loss exhibit sex-specific patterns and previous studies have yielded inconsistent findings regarding the patterns of fat-free mass changes after weight loss, which appear to be influenced by sex.[16–19] A preliminary study involving 52 participants who underwent weight loss over a 2-year period reported significant thigh mass loss, with no significant differences between sexes. However, this study faced several limitations, including insufficient data for KOA diagnosis, a small sample size, and no adjustments for confounders.[17] Moreover, in a study on the sex-specific effects of diet-induced weight loss on fat-free mass, Christensen et al. found that females show a greater decrease in fat-free mass.[16] In contrast, a few other studies have suggested that males typically lose fat mass and skeletal muscle mass at similar rates, while females tend to lose more fat mass than skeletal muscle mass.[18,19] Despite the insights provided by such studies, they did not account for detailed biomarkers that contribute to muscle quality, specifically intramuscular adipose tissue (Intra-MAT) and contractile percentage. Magnetic Resonance Imaging (MRI) has demonstrated strong efficacy in evaluating structural changes in thigh muscles and is widely used in KOA studies. Given the heterogeneity in the existing literature regarding sex-based differences in generalized muscle quality changes, the importance of thigh muscle changes in progression of KOA outcomes, and considering the promising role of MRI in detailed evaluation muscle changes, this study aimed to explore longitudinal changes in thigh muscle quality according to sex during > 5 % weight loss among participants with known baseline KOA.[17,20]

Methods

Data source

We utilized data from the longitudinal and multicenter cohort study of the Osteoarthritis Initiative (OAI) (2004–2015, clinicaltrials.gov identifier: NCT00080171, with details available at https://nda.nih.gov/oai/). According to the OAI protocol, 4796 male and female participants among all ethnic groups suffering from, or at risk of KOA in the age group of 45–79 years were recruited. Patients with MRI contraindications, inflammatory arthropathies, positive pregnancy tests, bilateral knee replacement surgery, and comorbid conditions were excluded from the OAI study. Fig. 1 provides an overview of participant selection process of this study. Provided with the details of the procedures and the aim of the study, all recruited participants provided their written informed consent. The HIPAA-compliant protocol of OAI has been approved by the ethics committees of all four centers involved in the study (approval code: 10–00532).[21]

Study population

From the OAI database, we included participants with the evidence of radiographic KOA, using the semi-quantitative Kellgren and Lawrence (KL) grading system, and participants graded ≥ 2 at the baseline visit were defined as having established KOA and included in the study. Participants with missing MRI data on either baseline or year-4 timepoint, missing KL grades, or without evidence of KOA at baseline radiography (KL grade < 2) were excluded. To further tailor the study sample, we included participants who experienced > 5 % reduction in their weight levels[10] over a 4-year follow-up period (defined as the calculated difference between baseline and 4th-year BMIs divided by the baseline Body Mass Index (BMI)). The 5 % threshold was established based on previous studies, suggesting it as indicative of a clinically significant weight loss.[9,22]

MRI acquisition and outcome measures

Thigh MRIs were acquired at four distinct clinical sites of the OAI using cross-calibrated 3.0-T MRI systems (Magnetom Trio, Siemens Healthcare). Fifteen continuous axial T1-weighted spin-echo images (thickness 5 mm), starting 10 cm above the distal femoral epiphysis and extending 7.5 cm proximally. In light of the differences in body height and thigh length, the axial slice in the area that represents 33 % of the femur bone's distal length was chosen for segmentation. Previous studies have demonstrated that the above selected slice accurately represents the volume of thigh muscles. Therefore, this particular slice was chosen to provide a precise representation of the thigh muscle composition.[23–26] Since longitudinal 2D assessment of muscle segmentation is sensitive to section selection, we registered selected sections using similarities in the key point features extracted by the Oriented FAST and Rotated BRIEF (ORB) method. Using a fully automated and validated deep learning algorithm for segmentation and interpretation of OAI thigh MRIs, previously introduced by our team,[27] we measured MRI-derived biomarkers of thigh muscle quality at baseline, year-2, and year-4. The outcomes were the Intra-MAT and contractile percentage of thigh muscles (quadriceps, adductors, flexors, sartorius, and total thigh) as well as intermuscular adipose tissue (Inter-MAT) between females and males (Fig. 2). Intra-MAT and Inter-MAT were defined as the area (mm^2) of fat-containing tissue pixels within and between the distinct muscles (i.e., quadriceps, adductors, flexors, sartorius), respectively. To measure these biomarkers, we used a validated Otsu intensity thresholding method on the images in the ImageJ platform.[28,29] The Intra-MAT and Inter-MAT were then determined by summing the white pixels, representing fat in T1-weighted images, within each segment following the thresholding of muscles and intermuscular tissue, respectively. These measurements were then multiplied by the pixel area (mm^2) to compute Cross-sectional area (CSA). These resultant variables have been widely utilized in previous studies.[28,30–32] The contractile percentage was defined as the ratio of non-fat muscle CSA to total muscle CSA:

$$\text{Contractile \%} = \frac{\text{Muscle CSA} - \text{Muscle intra} - \text{MAT CSA}}{\text{Muscle CSA}}$$

Statistical analysis

Statistical analyses were performed using the R software version 4.0.3 (haven, mice, lme4, lmerTest, and tableone packages). Multilevel linear mixed-effect regression models were used to assess the association between dependent outcome measures (the baseline

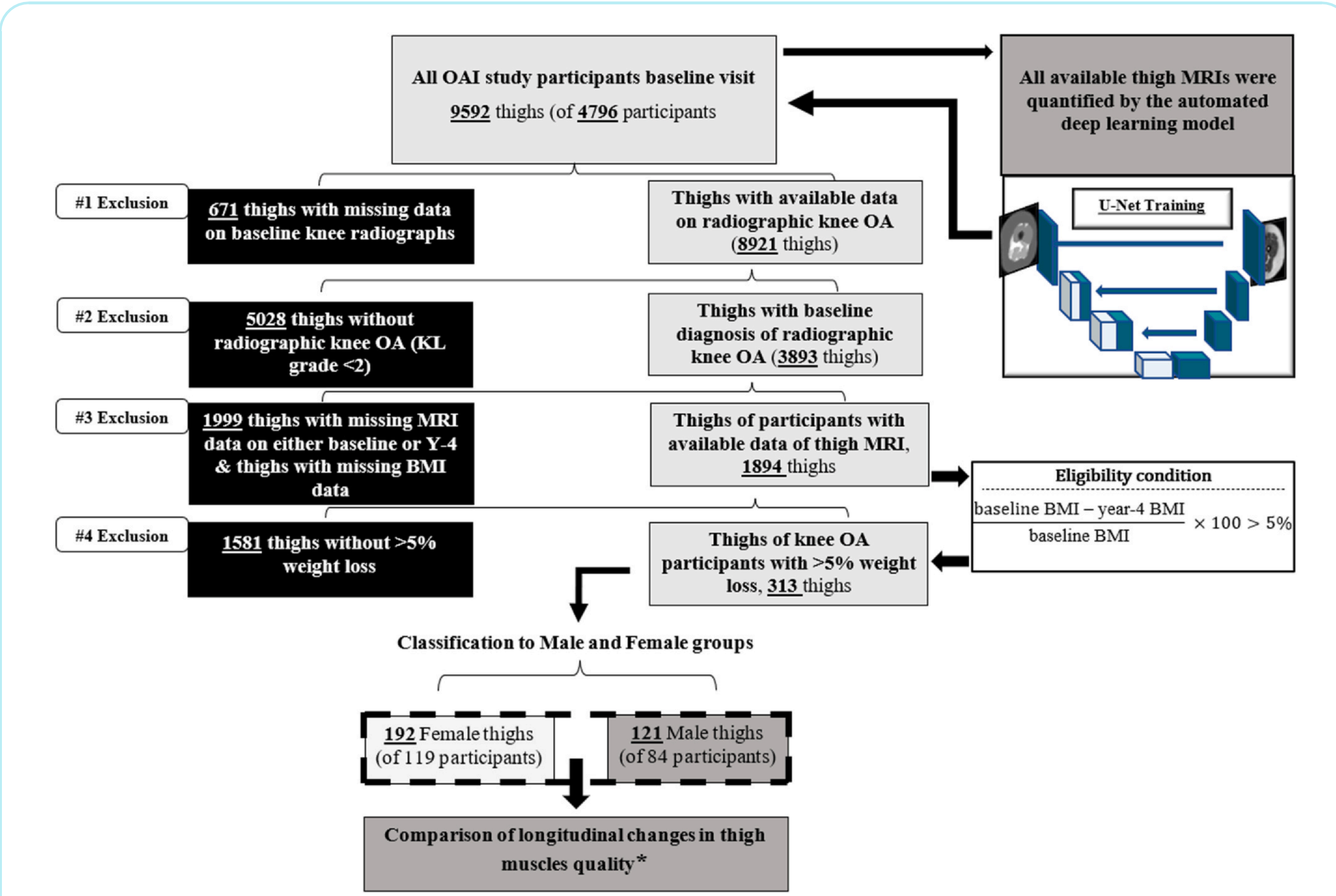

Fig. 1 Osteoarthritis and Cartilage

Flowchart representing the stepwise selection process. KL: Kellgren and Lawrence, OA: osteoarthritis, Y-4: Year-4. * Study outcomes.

and year-4 levels of Intra-MAT, Inter-MAT, and contractile percentage of thigh muscles) and sex (as a bivariate male/female variable) as the independent predictor). We performed the analyses for the total thigh, as well as separately for individual thigh muscles (quadriceps, adductors, flexors, sartorius). For each participant ID, a random intercept was considered to account for similarities within the participant (owing to the inclusion of knees/thighs from both sides in 54.1 % of the participants). Our analysis was mainly carried out using data from thigh muscles, instead of individual participants. This approach was chosen to adjust the localized periarticular effects of the ipsilateral KOA status on the thigh muscles. The analysis was adjusted for potential confounders at baseline, including participants' characteristics (age, race, BMI), risk factors (physical activity measured by Physical Activity for Elderly Scale (PASE) score, smoking history, alcohol use, diet composition), symptomatic and structural status of the knee joint (Western Ontario and McMaster Universities Osteoarthritis (WOMAC) pain score, KL grade, medial Joint space narrowing (JSN) grade), as well as 4-year BMI change. The data on diet was measured by Block Brief 2000 Food Frequency Questionnaire. The assumptions of linear mixed-effect regression model (linearity, homogeneity of variance, normal distribution of residuals, normality [data were transformed in case of nonnormal distribution]) were assessed.

The method of Benjamini and Hochberg was employed to monitor the false discovery rate (FDR) and adjust p-values in light of multiple comparisons. A two-tailed FDR-adjusted p-value less than 0.05 was deemed indicative of a statistically significant difference.

Sensitivity analysis

We conducted two sensitivity analyses to test the robustness of our results. First, our primary study examined the 4-year changes in thigh muscle biomarkers among participants who experienced a weight loss of > 5 % during the same 4-year period. In this analysis, we also explored the 2-year changes in these biomarkers among participants who had a weight loss of more than 5 % over the concurrent 2-year period. For the second sensitivity analysis, as our main study was inclusive to both thighs in a subset of participants with bilateral knee OA, we modified our main inclusion criteria to one thigh per participant This resulted in two separate analyses, each focusing on the right and left thighs of knees affected by ipsilateral OA.

Results

Participants' characteristics

After applying the inclusion/exclusion criteria to OAI participants, we included a total of 313 thighs in our study. This comprised 192 thighs from female participants (119 individuals) and 121 thighs

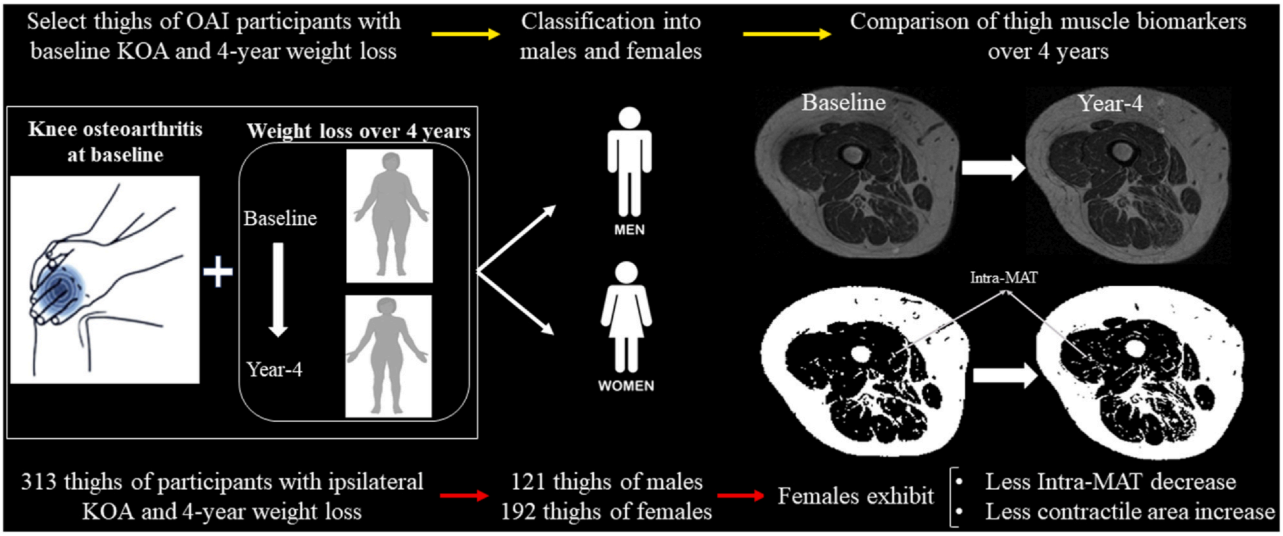

Fig. 2 Osteoarthritis and Cartilage

Schematic diagram representing the timing and assessments of this study. Biomarkers of thigh muscle quality were measured at baseline and year-4. These outcomes were compared between males and females with radiographic knee osteoarthritis at baseline and > 5 % reduction in BMI level over a 4-year period. OAI: osteoarthritis initiative, KOA: knee osteoarthritis, MRI: magnetic resonance imaging.

from male participants (84 individuals). The details of the study selection process are illustrated in Fig. 2. Notably, except for the sartorius, the baseline contractile percentage of thigh muscles (quadriceps, adductors, flexors, and total thigh muscles) were comparable between males and females (p-values > 0.05), indicating similar baseline muscle quality between the sexes. Additionally, the female and male groups exhibited a comparable degree of weight loss, as evidenced by the percentage decrease in their BMI levels (females: −9.72 ± 4.38, males: −8.83 ± 3.64, p = 0.121).

Male and female groups did not significantly differ in baseline participant characteristics and risk factors (including race, baseline BMI, smoking history, and alcohol use) and symptomatic and structural KOA outcomes at baseline (including history of knee traumatic injury, WOMAC pain score, and KL grade). However, the between-group analysis of baseline characteristics revealed significant differences between males and females in participants' age, PASE score, and diet composition. Seemingly, the male and female groups showed a significant difference in the baseline medial JSN grade. An overview of the participants' characteristics is provided in Table I.

Longitudinal changes in MRI-derived biomarkers of thigh muscles among males and females

Throughout the 4-year study period, we observed a decrease in Intra-MAT and an increase in the contractile percentage across all muscle groups, including quadriceps, adductors, flexors, sartorius, and total thigh - in both males and females. Additionally, both sexes exhibited an increase in Inter-MAT over the course of the 4-year weight loss period. Detailed findings are presented in Table II.

Comparison of longitudinal changes in MRI-derived biomarkers of thigh muscles between males and females

After accounting for potential confounders, linear mixed-effect regression models revealed that, compared to males with KOA, females with KOA exhibited a less degree of longitudinal decrease in Intra-MAT in quadriceps (change difference, 95 %CI: 394.50 mm^2/4-year, 269.57 to 519.43), adductors (change difference, 95 %CI: 107.01 mm^2/4-year, 53.18 to 160.83), flexors (change difference, 95 %CI: 195.01 mm^2/4-year, 87.27 to 302.75), sartorius (change difference, 95 %CI: 86.93 mm^2/4-year, 59.82 to 114.04), and total thigh muscles (change difference, 95 %CI: 783.44 mm^2/4-year, 505.70 to 1061.19) during a weight loss of > 5 % over 4 years (Table II). However, the change in Inter-MAT CSA was consistent between males and females throughout the 4-year weight loss period (change difference, 95 %CI: 41.69 mm^2/4-year, −56.37 to 139.74).

After adjusting for potential confounders, in females with KOA, > 5 % weight loss over 4 years was accompanied with a less degree of longitudinal increase in contractile percentage in quadriceps (change difference, 95 %CI: −5.1 %, −7.4 to −2.7), sartorius (change difference, 95 %CI: −12.9 %, −18.9 to −7.0), and total thigh muscles (change difference, 95 %CI: −3.9 %, −6.5 to −1.4), compared to the males. However, the difference in contractile percentage between females and males with KOA in adductors and flexors did not reach statistical significance after 4 years of follow-up (Table II).

Sensitivity analysis

Sensitivity analyses indicated that the results remained consistent when either changing the study period to 2 years (Supplemental Table 1) or when selecting a single thigh per participant (Supplemental Tables 2 and 3).

Discussion

This study showed that compared with males with KOA, females with KOA showed a less degree of longitudinal decrease in Intra-MAT and longitudinal increase in contractile percentage of thigh muscles, during a weight loss of > 5 % over 4 years. Notably, the mentioned results were observed despite similar degrees of weight loss between males (8.83 %) and females (9.72 %). The observed alterations in muscle biomarkers could be attributable to sex

Variables	Females	Males	P-value[*]
	N = 192	N = 121	
Subject demographic characteristics and risk factors			
Age (years) [mean (SD)]	64.23 (8.98)	61.56 (9.56)	**0.030**
Race (non-white) [N (%)][ϕ]	55 (32.54)	35 (30.43)	0.831
Baseline BMI (kg/m^2) [mean (SD)]	29.77 (5.63)	29.88 (4.08)	0.897
4-year percent change in BMI [mean (SD)][†]	-9.48 (3.96)	-8.81 (3.66)	0.121
PASE score [mean (SD)]	144.79 (65.48)	170.18 (90.01)	**0.009**
Smoking history (positive) [N (%)]	4 (2.37)	44 (38.26)	0.257
Alcohol use (positive) [N (%)]	126 (74.56)	95 (82.61)	0.712
Baseline diet composition (daily % of calories)[‡]			
Protein (%) [mean (SD)]	18.81 (3.63)	17.67 (2.96)	0.085
Carbohydrate (%) [mean (SD)]	49.39 (8.97)	46.64 (10.09)	**0.008**
Fat (%) [mean (SD)]	34.61 (7.44)	37.77 (8.12)	**< 0.001**
Symptomatic and structural KOA outcomes			
History of knee traumatic injury	56 (33.1)	35 (30.4)	0.962
WOMAC pain score [mean (SD)]	16.55 (16.79)	13.76 (17.53)	0.583
KL grade [N (%)]			0.439
Grade 2	115 (68.05)	77 (66.96)	
Grade 3	47 (27.81)	29 (25.21)	
Grade 4	7 (4.14)	9 (7.82)	
Medial JSN grade [N (%)]			**0.009**
Grade 0	85 (50.29)	37 (32.17)	
Grade 1	53 (31.36)	45 (39.13)	
Grade 2	29 (17.16)	26 (22.61)	
Grade 3	2 (1.18)	7 (6.08)	
Contractile percentage of thigh muscles			
Quadriceps [mean (SD)]	0.90 (0.12)	0.88 (0.11)	0.264
Adductors [mean (SD)]	0.82 (0.15)	0.81 (0.16)	0.585
Flexors [mean (SD)]	0.85 (0.14)	0.84 (0.15)	0.449
Sartorius [mean (SD)]	0.74 (0.27)	0.67 (0.30)	**0.026**
Total thigh muscles [mean (SD)]	0.87 (0.12)	0.85 (0.13)	0.278

Abbreviations: BMI: Body Mass Index, JSN: Joint space narrowing, KL: Kellgren and Lawrence, PASE: Physical Activity for Elderly Scale, SD: Standard Deviation, WOMAC: Western Ontario and McMaster Universities Osteoarthritis.

[*] Data are presented in numbers of thighs. Linear mixed-effect and generalized linear mixed-effect regression models were used for comparison to account for within-subject similarities in the proportion of participants that had both of their thighs included.

[ϕ] Participants' race and ethnicity included Asian, Black, White, none of these, and not reported. Race of participants was categorized as white and non-white considering the small number of participants in each non-white race group.

[†] 4-year BMI change was defined as: BMI change% = $\frac{\text{year} - 4\text{BMI} - \text{baseline BMI}}{\text{baseline BMI}} \times 100$

[‡] The daily percentage of calories derived from proteins, carbohydrates, and fats was measured and reported using the Block Brief 2000 Food Frequency Questionnaire (alcoholic beverages were not included in the calculation and were excluded from denominator).

Table I Osteoarthritis and Cartilage

Demographic and clinical characteristics of the study population according to sex.

differences, as potential confounding factors such as baseline characteristics of participants, risk factors, diet composition, the degree of weight loss, and KOA outcomes were considered.

In line with the findings of this study, previous studies have shown that weight loss may be associated with an increase in fat-free mass.[13,15] Weight loss, while being a primary treatment strategy for managing KOA particularly in overweight patients,[9,10,33–35] may also have additional effects on thigh muscles. To compare the change in muscle composition between males and females who lost weight by > 5 % over 4 years, and to distinguish it from the local periarticular effects of KOA, we adjusted the results for symptomatic and radiographic KOA outcomes measured at the baseline. We found that changes in thigh muscle quality persist even after adjustment, indicating that these sex differences may be related to the direct effect of > 5 % weight loss over 4 years on the thigh muscles' composition, rather than the outcomes of KOA. A strong body of evidence supports the notion that thigh muscle quality is associated with the development and progression of KOA,[27,36] and therefore, it appears crucial to maintain thigh muscle quality when recommending weight loss in the context of KOA management. Resistance training exercises and use of protein-rich diet have been shown to promote protein synthesis and muscle maintenance.[37,38] These interventions, which are already in widespread use, have been found to improve thigh muscle quality.[11,12,39] The findings of this study suggest that a more targeted approach to these interventions, with a specific focus on enhancing muscle quality in both males and females during weight loss efforts, could provide significant clinical benefits and could lead to more effective weight loss strategies. Finally, prior research has extensively explored sex-specific interventions for weight loss to enhance outcomes in KOA.[40–42] Discussions on sex-specific strategies to preserve and enhance muscle quality during weight loss have revealed that strength training is more beneficial for females with KOA, while aerobic

Outcome variables	4-year change among thighs of males (95 % CI)	4-year change among thighs of females (95 % CI)	Adjusted rate of change difference (95 % CI)*	P-value
Quadriceps				
Intra-MAT CSA (mm^2/4-year)	-493.08 (−615.66 to −370.50)	-186.68 (−258.83 to −114.53)	394.50 (269.57 to 519.43)	**< 0.001**
Contractile percentage (%/4-year)	7.4 (5.5 to 9.4)	3.4 (1.9 to 4.9)	-5.1 (−7.4 to −2.7)	**< 0.001**
Adductors				
Intra-MAT CSA (mm^2/4-year)	-219.48 (−276.34 to −162.62)	-124.33 (−154.27 to −94.39)	107.01 (53.18 to 160.83)	**0.003**
Contractile percentage (%/4-year)	13.0 (10.1 to 15.8)	11.0 (8.7 to 13.2)	-3.8 (−7.2 to −0.3)	0.096
Flexors				
Intra-MAT CSA (mm^2/4-year)	-445.35 (−553.71 to −336.99)	-255.46 (−316.85 to −194.06)	195.01 (87.27 to 302.75)	**0.006**
Contractile percentage (%/4-year)	10.2 (7.6 to 12.7)	8.3 (6.3 to 10.2)	-1.7 (−4.7 to 1.3)	0.379
Sartorius				
Intra-MAT CSA (mm^2/4-year)	-128.29 (−156.49 to −100.10)	-66.40 (−81.90 to −50.90)	86.93 (59.82 to 114.04)	**< 0.001**
Contractile percentage (%/4-year)	25.7 (20.3 to 31.1)	17.6 (13.9 to 21.2)	-12.9 (−18.9 to −7.0)	**0.001**
Total thigh				
Intra-MAT CSA (mm^2/4-year)	-1286.20 (−1576.29 to −996.11)	-632.87 (−791.31 to −474.44)	783.44 (505.70 to 1061.19)	**< 0.001**
Inter-MAT CSA (mm^2/4-year)	224.63 (147.87 to 301.40)	303.38 (238.03 to 368.72)	41.69 (−56.37 to 139.74)	0.510
Contractile percentage (%/4-year)	9.7 (7.5 to 12.0)	6.7 (5.0 to 8.3)	-3.9 (−6.5 to −1.4)	**0.019**

Abbreviations: CI: Confidence interval, CSA: Cross-sectional area, Intra-MAT: Intra-muscular adipose tissue, KOA: Knee osteoarthritis.
* Multilevel mixed-effect regression models were used to assess the difference in changes of muscle biomarkers between the sex groups. Models were adjusted for potential confounders at the study baseline, including age, race, physical activity (PASE score), smoking history, alcohol use, BMI level, 4-year BMI change, history of knee traumatic injury, WOMAC pain score, KL grade, and JSN grade. Bolded results are those that their P-values remained below 0.05 after False discovery rate (FDR) correction for multiple comparisons using the Benjamini and Hochberg method.

Table II

Osteoarthritis and Cartilage

Comparison of longitudinal 4-year changes in MRI-derived biomarkers of thigh muscle composition between thighs of males and females with baseline KOA and 4-year weight loss.

exercises are more advantageous for males with KOA.[37] Supporting this, Campbell et al. highlighted the positive impact of a high-protein diet during resistance training on the maintenance of muscle quality and fat-free mass during weight loss in females.[43] These examples emphasize the importance of creating sex-specific strategies for preserving and enhancing muscle quality during weight loss, setting the stage for future research to introduce such interventions.

Despite the established role of thigh muscle quality and its modifiability, the literature remains limited in studies that considered and assessed muscle quality changes in patients with KOA during weight loss. In a preliminary study by Steidle-Kloc et al., 52 subjects who experienced weight loss over a 2-year period were examined to understand sex-specific changes in thigh muscle CSA in response to weight loss.[17] The study found significant loss in the thigh mass during weight loss, with no notable sex differences. However, the study had several limitations, including a lack of KOA evidence in over half of the participants, a small and unevenly distributed sample size, and a lack of adjustment for potential confounders. The study also analyzed total thigh muscle groups as a whole, rather than accounting for different muscle groups. Our study aimed to address these limitations by using a larger sample size confined to the KOA group of participants, almost evenly distributed between males and females. We also extended the longitudinal follow-up period to 4 years and adjusted for a broad list of potential confounders. Furthermore, we compared the changes in muscle quality between males and females who lost weight by > 5 % over 4 years in different muscles in the thigh area to improve statistical power and generate more interpretable results. Finally, despite the insights provided by this study and other similar ones, they did not account for other biomarkers that contribute to muscle quality, specifically Intra-MAT and contractile percentage. In our current study, we have taken these biomarkers into consideration. Our findings suggest that weight loss could potentially improve thigh muscle quality, with these benefits appearing to be more pronounced in males. To validate these sex differences in the weight loss context, further research is necessary.

Although the precise mechanisms underlying sex differences in Intra-MAT and contractile percentage response to weight loss are not truly understood, the findings of this study may be partly explained by the interplay between sex-specific physiologic and hormonal differences.[44–46] Moreover, behavioral and environmental factors should be considered as potential contributors to the different change of thigh muscle quality in females during weight loss. Tsai et al. demonstrated that males, when attempting to lose weight, tend to increase their exercise levels and decrease their fat intake, while females are more likely to participate in weight loss programs, use prescription diet pills, and follow special diets.[47] One of the reasons could be that males are culturally encouraged to have more athletic and muscular physique.[48,49] Meanwhile, research indicates that training exercises (particularly strength training) and specific diets can help preserve and enhance fat-free mass and contractile percentile during weight loss.[50,51] These lifestyle differences between males and females may account for the varying changes observed in thigh muscle quality during weight loss. Therefore, future clinical trials are warranted to compare muscle changes during weight loss when both groups employ the same weight loss methods.

Several limitations are present in this study. First, weight loss-associated changes in muscle quality are influenced by the method of weight loss. However, this study does not account for such methods (i.e., diet, physical activity, unintended weight loss, etc.) as these were not measured in the OAI. We attempted to reduce the confounding effects of physical activity and diet on our results by adjusting for physical activity, as measured by the PASE score, and diet composition, as determined by the baseline daily percentage of calories from proteins, carbohydrates, and fats. However, the PASE is specifically designed for measuring physical activity of individuals aged 65 and above, while a substantial portion of patients in the OAI dataset and in this study are under the age of 65. As such, PASE may not be the most suitable tool for assessing their level of physical activity. Regarding diet, the OAI only provides baseline data on diet composition. Given the potential significant changes in dietary patterns during the weight loss period, it would be beneficial to consider longitudinal data as well. Further studies are needed to address this issue. Second, while we hypothesized that the observed sex difference in the change of thigh muscle quality could be partially attributed to physiological and hormonal variations between males and females, the OAI database does not provide any serum biomarkers to confirm such a mediating effect. This limitation highlights the need for future studies to analyze available OAI serum samples to further investigate this aspect. Third, given that the OAI dataset was initially obtained with the intention of studying KOA, any retrospective post-hoc analyses conducted on this dataset could potentially be subject to selection bias. Fourth, we implemented a single axial slice of the thigh MRI on a specific anatomical location at 33 % distal length of the femur bone to calculate the outcomes while the actual measures of the muscle quality can vary in different slices. Although it was not possible to interpret the MRI of the thigh at other levels, previous research has indicated that muscle CSAs computed at this level have a strong correlation with the 3D volume of the muscle.[23–26] Finally, we did not implement a no-weight loss control group in this study. Therefore, the current study cannot determine if the observed pattern of thigh muscle changes is attributed to weight loss, or the sex itself.

In conclusion, this study found that female participants with diagnosed KOA show less beneficial changes in thigh muscle quality compared with males during a weight loss of > 5 % over 4 years. These findings pave the way for future studies to explore the role of underlying mechanisms (notably, physiologic, hormonal, and behavioral determinants) in the observed changes in muscle quality due to weight loss. The results of this study showed that disease-modifying interventions should be designed and recommended in an individualized and sex-specific manner to maximize the benefits for thigh muscle quality, and subsequently, KOA. Future endeavors may shed light on the association between sex-specific changes in muscle quality and sex-specific clinical manifestations mediated by weight loss. Also, future studies implementing a no-weight loss control group can determine if the observed changes can be attributed to weight loss or the direct effect of sex on the thigh muscle quality.

Ethics approval

The medical ethics review boards of the University of California, San Francisco (Approval Number: 10–00532) and the four clinical centers of osteoarthritis initiative project recognized the project as Health Insurance Portability and Accountability Act (HIPAA)-compliant. This project was in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments and all individuals gave their informed consent prior to their inclusion in the study.

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Data availability

The de-identified clinical and demographic information of participants is publicly available at the osteoarthritis initiative project data repository at https://oai.nih.gov. The R codes used in this work are available from the corresponding author upon reasonable request.

Conflict of interest

AG is a shareholder of BICL and consultant to Pfizer, TissueGene, Pfizer, Novartis, Coval, ICM, TrialSpark, and Medipost. FWR is shareholder of BICL, LLC, and consultant to and Grünenthal GmbH. SD reported that he received funding from Toshiba Medical Systems (for consultation) and grants from GERRAF and Carestream Health (for a clinical trial study). The views expressed are those of the authors and not necessarily those of the National Health Service, the NIHR, or the Department of Health. None of the authors has any conflicting personal or financial relationships that could have influenced the results of this study. Other authors declare that they did not have any competing interests.

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In preparing this manuscript, osteoarthritis initiative project publicly available datasets were used. The results of this work do not necessarily reflect the opinions of the osteoarthritis initiative project investigators, the NIH, or the private funding partners.

Author contributions

All authors participated in the study design, interpretation of results, and drafting the manuscript or critically revising it for relevant intellectual content. Kamyar Moradi designed the study, performed the data analysis and contributed to writing the original and final draft and revising it critically for intellectual content. Bahram Mohajer contributed to data analysis and methodology of the study. Soheil Mohammadi contributed to writing the original and final draft and revising it critically for intellectual content. Ali Guermazi, Hamza Ahmed Ibad, Frank W. Roemer, Xu Cao, and Thomas M. Link contributed to writing the final draft and revising the manuscript. Shadpour Demehri supervised and encouraged the study and contributed to data analysis, writing the final draft, and revising it critically for important intellectual content.

Patient involvement

Participants have given informed consent before participating in the Osteoarthritis Initiative (OAI) project. It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.joca.2024.05.013.

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