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Skeletal Muscle Composition, Power, and Mitochondrial Energetics in Older Men and Women With Knee Osteoarthritis

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Objective. Our objective was to investigate the overall and sex-specific relationships between the presence and severity of knee osteoarthritis (KOA) and muscle composition, power, and energetics in older adults.

Methods. Male and female patients (n = 655, mean ± SD age 76.1 ± 4.9 years; 57% female) enrolled in the Study of Muscle, Mobility, and Aging completed standing knee radiographs and knee pain assessments. Participants were divided into three groups using Kellgren-Lawrence grade (KLG) of KOA severity (0–1, 2, or 3–4). Outcome measures included whole-body muscle mass, thigh fat-free muscle (FFM) volume and muscle fat infiltration (MFI), leg power, specific power (power normalized to muscle volume), and muscle mitochondrial energetics.

Results. Overall, the presence and severity of KOA is associated with greater MFI, lower leg power and specific power, and reduced oxidative phosphorylation (P trend < 0.036). Sex-specific analysis revealed reduced energetics only in female patients with KOA (P trend < 0.007) compared to female patients without KOA. In models adjusted for age, sex, race, nonsteroidal anti-inflammatory drug administration, site or technician, physical activity, height, and participants with abdominal adiposity with KLG 3 to 4 had greater MFI (mean 0.008%, 95% confidence interval [CI] 0.004%–0.011%) and lower leg power (mean –51.56 W, 95% CI –74.03 to –29.10 W) and specific power (mean –5.38 W/L, 95% CI –7.31 to –3.45 W/L) than those with KLG 0 to 1. No interactions were found between pain and KLG status. Among those with KOA, MFI and oxidative phosphorylation were associated with thigh FFM volume, leg power, and specific power.

Conclusion. Muscle health is associated with the presence and severity of KOA and differs by sex. Although muscle composition and power are lower in both male and female patients with KOA, regardless of pain status, mitochondrial energetics is reduced only in female patients.

INTRODUCTION

Osteoarthritis (OA) increases in prevalence with advancing age,[1] frequently affects the knee causing knee pain,[2] and is a leading cause of immobility and disability worldwide.[3–5] The ability of muscle to generate sufficient force to support physical function is compromised by age- and disease-related changes in muscle mass, composition, and cellular functions.[6] These changes may increase loading of the knee joint and, in persons with knee OA (KOA), may accelerate progression of knee pain, joint tissue damage, and loss of mobility and initiate a vicious cycle with further declines in muscle funcion and strength. Clinical OA

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characteristics have shown to be distinct between male and female patients.[7] However, few studies to date have investigated sex-specific myocellular adaptations associated with KOA. Additionally, studies of the effect of muscle properties on reduced mobility outcomes in older adults with KOA are scarce, constituting a gap in our understanding of the factors that may influence reduced mobility and disability.[8,9]

Poor muscle characteristics are associated with KOA.[8,10,11] Cross-sectional comparisons of healthy controls and study participants with KOA report differences in muscle fiber composition, intermuscular and intramuscular adiposity, extracellular matrix content, and quadriceps muscle strength and power.[8,11,12] These differences may be confounded by the higher body adiposity commonly seem in individuals with KOA. Studies that perform a comprehensive investigation of skeletal muscle health in KOA and that investigate the influence of adiposity and other relevant variables on the association between muscle health and KOA are needed. Although radiographic KOA is characterized by structural joint changes, symptomatic or clinical KOA is characterized by the presence of knee pain. Although KOA is frequently accompanied by knee pain, the reason why some individuals do not report joint pain is not completely understood. Specifically, the myocellular factors associated with the presence of pain are poorly understood and deserve further investigation.

In skeletal muscle, mitochondria produce the ATP needed for muscle contraction and mobility. Muscle mitochondrial energetics is influenced by aging,[13,14] obesity,[15,16] and physical activity levels.[17,18] In older adults, muscle mitochondrial energetics is associated with leg power,[19] physical performance,[20,21] and fatigability.[22] Despite the well-established role of mitochondrial energetics in muscle health, it is unclear whether the reduced muscle strength and power commonly observed in older adults with KOA[12] are accompanied by impairments in muscle mitochondrial energetics.

In this ancillary study from the Study of Muscle, Mobility, and Aging (SOMMA), we examined the overall and sex-specific relationship between the presence and severity of KOA and skeletal muscle composition, leg power, and muscle mitochondrial energetics in a cohort of healthy older adults. We also explored the influence of knee pain on these associations. We hypothesized that older adults with KOA would have decreased leg power and energetics and increased muscle fat infiltration (MFI) when compared to study participants without KOA, and that these impairments would be associated with KOA severity and the presence of pain. We also hypothesized that the distinct clinical manifestation of KOA in male and female patients would be associated with distinct muscle health characteristics.

PATIENTS AND METHODS

Study design and population. SOMMA aims to determine the biologic processes that contribute to changes in mobility and fitness with aging.[23] The study is being conducted at two clinical sites (University of Pittsburgh and Wake Forest University School of Medicine), a biorepository (AdventHealth Translational Research Institute), and the San Francisco Coordinating Center (California Pacific Medical Center Research Institute). Study participants were included in SOMMA if they were ≥70 years old and able to complete a 400 m walk at ≥0.6 m/s (4 m). Study participants had to be free of life-threatening disease and had no contraindications to magnetic resonance imaging (MRI) or tissue collection. Individuals were excluded from the study if they reported an inability to walk one-fourth of a mile or climb a flight of stairs, an active malignancy, or advanced chronic disease.[23]

This ancillary cross-sectional study enrolled SOMMA participants who returned for the first annual visit and consented to completing a standing knee radiograph. Those who completed knee radiographs and pain assessments were included in the analysis. Participants provided written informed consent, and the study was approved by the Western Institutional Review Board Copernicus Group (no. 20180764) for all participating sites.[23,24]

Radiographic and symptomatic KOA. Bilateral, fixed-flexion, weight-bearing posteroanterior knee radiographs were obtained at the SOMMA one-year follow-up visit using previously published methods.[25] The presence and severity of KOA was determined with Kellgren-Lawrence grades (KLGs) of radiographic KOA severity[26] (scale 0–4), and the extent of medial and lateral joint space narrowing were scored centrally based on the Osteoarthritis Research Society International atlas of individual radiographic features.[27,28] Reproducibility of the readings of KLG were tested by independent readings of 50 radiographs performed by one reader (TML) from patients in whom one or both knees were scored with a KLG of 1 or 2 by the initial reader (NEL). The reliability of these readings was good, with a weighted kappa for interrater reliability of 0.75 (95% confidence interval [CI] 0.69–0.79]. Interreader reliability for the presence or absence of radiographic KOA was also good, with a simple kappa of 0.72 (95% CI 0.65–0.79).

Participants were assigned into one of three groups according to the presence and severity of radiographic KOA determined with KLGs: KLG 0 to 1 (normal to doubtful), KLG 2 (mild), and KLG 3 to 4 (moderate to severe). We combined study participants with KLG 3 and KLG 4 into one group because there were few participants with KLG 4 (n = 92), and statistical comparisons between the two KLG groups showed similar muscle health characteristics (data not shown). Additionally, study participants were placed into a group according to the results of their worse knee radiographic score. We used a multiple-choice pain questionnaire to identify symptomatic KOA, which was defined by the presence of knee pain monthly, weekly, or daily while going up and down the stairs

and/or walking on a flat surface and/or having knee pain lasting at least 1 month in the last 12 months.[12]

General study measurements. SOMMA baseline assessments were collected at visits over several days and included self-reported information on birth date, sex, race, ethnicity, medical history, and prescription medications.[23] Participants self-reported race and ethnicity from a fixed set of categories. Study participants provided information on all prescription medication taken in the 30 days before the study visits. For this analysis we used information provided by the study participants on prescriptions of both oral and topical nonsteroidal anti-inflammatory drug (NSAID) preparations. Self-reported mobility was assessed with the mobility assessment tool-short form.[29] The Short Physical Performance Battery (SPPB) test was used to assess lower extremity function.[30] Gait speed was assessed with a 400-meter walk.[24] Cardiorespiratory fitness (VO_2 peak) was assessed by a standard cardiopulmonary exercise test using a modified Balke or manual protocol.[24] Physical activity was monitored by activPAL4 (micro; PAL Technologies Ltd) worn on the right thigh for seven consecutive 24-hour periods. Average number of steps per day was used as a quantitative measure of physical activity.[31] Height was measured on stadiometers, and weight was measured on digital scales.

Measurement of whole-body muscle mass. Whole-body muscle mass (kg) was measured using the D_3-creatine (D_3Cr) dilution method, as previously described.[32] Briefly, three to six days after patients took an oral dose of deuterated creatine, total body creatine pool sizes were calculated from urine measures using a published algorithm. The D_3Cr dilution method has been validated and is correlated with MRI-derived muscle volume[33] at r = 0.87, $P < 0.0001$.

Measurement of thigh muscle volume and fat infiltration. MRI was used to assess volume of visceral adipose tissue (VAT), abdominal subcutaneous adipose tissue (ASAT), thigh fat free muscle (FFM), anterior thigh FFM, and anterior thigh MFI. Total abdominal adipose tissue volumes were calculated by adding VAT and ASAT volumes. MRI scans were obtained at the baseline visit, processed with Dixon water-fat imaging using AMRA Researcher (AMRA Medical AB), and analyzed as previously described.[34] Analyses included manual quality control by a masked trained operator.

Measurement of knee extensor peak power. Knee extensor peak power (the product of the force and velocity of muscle contraction, watts) was assessed using a Keiser pneumatic resistance device (A420 model; Keiser Sports Health Equipment), as described.[24] Participants seated with the leg at a 90° angle were instructed to press their leg as fast as possible through a full range of motion. Two repetitions were performed as a warm-up to leg press strength and power testing, and then participants completed two trials for each intensity (40%, 50%, 60%, and 70%; one repetition maximum), with 30 seconds of rest between each trial at the same level of resistance and one minute of rest between each increase in resistance. The test was discontinued if pain or discomfort developed. Results represent the average of peak power collected from both legs. Thigh-specific power was defined as peak power per unit of total thigh FFM volume.[12]

Assessment of in vivo maximal mitochondrial ATP production. Quadriceps maximal mitochondrial ATP production (ATPmax) following an acute bout of knee extensor exercise was determined in vivo using31 phosphorous nuclear magnetic resonance spectroscopy.24 The exercise protocol was performed in a 3-T MR magnet (Prisma or Skyra Siemens Medical System; Siemens Healthineers) and consisted of a first bout of repeated isometric knee extension (30 seconds) against the resistance of an ankle strap. A subsequent bout was adjusted for the length of time of muscle contractions (18–36 seconds) based on the first bout to achieve adequate phosphocreatine breakdown without the accumulation of lactate. The average coefficient of variation for duplicates of ATPmax assessment was 9.9% across both clinic sites.

Muscle biopsy procedure and assessment of mitochondrial respiration. A percutaneous biopsy was obtained from the middle region of the vastus lateralis under local anesthesia using a Bergstrom canula with suction,[35] as previously described.[23] Approximately 20 mg of muscle tissue was placed in ice-cold biopsy preservation media preservation media[24] and immediately transferred to the laboratory for fresh assessments of mitochondrial respiration.

Permeabilized myofiber bundles of approximately 2 to 3 mg were prepared.[24] Mitochondrial respiration was evaluated by high-resolution respirometry (Oxygraph-2k, Oroboros Instruments). Measurements were performed in duplicate, at 37°C, in the oxygen range of 400 to 200 μ*M*, using MiR05 supplemented with Blebbistatin. Maximal complex I- and II-supported oxidative phosphorylation (OXPHOS) was measured in the presence of pyruvate, malate, glutamate, adenosine diphosphate, cytochrome c, and succinate.[19] Steady state O_2 flux for each respiratory state was determined and normalized to fiber bundle wet weight using Datlab 7.4 software (Oroboros Instruments). The average coefficient of variation for duplicates of OXPHOS was 11.5% across both clinical sites.

Statistical analyses. Study participant characteristics were compared in participants with KLG 0 to 1, 2, and 3 to 4 using linear regression unadjusted mean models (*P* for trend was calculated). ANOVA for continuous variables, Kruskal Wallis tests for continuous variables with skewed distributions, and

chi-square tests for categorical variables were run comparing KLG and pain groups (KLG 0–1 and no pain; KLG 0–1 and pain; KLG 2 and no pain; KLG 2 and pain; KLG 3–4 and no pain; and KLG 3–4 and pain). Unadjusted and multivariate linear regression models were then performed to compare the KLG 0–1 group to KLG 2 and KLG 3–4 groups. Model 1 included age, sex, race, administration of NSAIDs, physical activity, and clinical site or technician. Model 2 included variables in model 1, height, and total abdominal adipose tissue volume. Separate regression models were run to test for a linear trend across the three categories of the predictor variable for each outcome variable. All analyses were performed on the entire cohort and then separately for male patients and female patients. Tests for interactions between KLG and knee pain were performed. A significance of $P < 0.10$ was considered as a reason to stratify by knee pain. Pearson correlations coefficients were also calculated to assess the association between muscle intrinsic characteristics and muscle volume and power among those with KOA. All analyses were completed in SAS 9.4 (SAS Institute, Inc).

RESULTS

Cohort characteristics. From the 846 SOMMA participants who completed the study year-one visit, 655 completed knee pain assessments, consented to obtain a knee radiograph, and were included in the present analysis (Figure 1). Participants who didn't have a knee radiograph obtained and who had bilateral total knee replacement were excluded from this ancillary study. Participants were a mean ± SD age of 76.1 ± 4.9 years, 57% were female, and 86% were White. The mean ± SD body mass index (BMI) was 27.5 ± 4.4, and the mean ± SD physical activity was 6,972 ± 3,259 steps per day. Approximately 9.3% of the total cohort were prescribed NSAIDs.

Participant characteristics by radiographic KOA. Study participant characteristics were compared in participants with KLG 0 to 1, 2, and 3 to 4 using linear regression unadjusted mean models (*P* trend reported). Compared to participants with normal and doubtful KLGs (0–1), participants with mild (2) and moderate to severe (3–4) KLGs had higher BMIs ($P < 0.001$), were less physically active ($P < 0.001$), had lower cardiorespiratory fitness ($P < 0.001$), and were prescribed more NSAIDs ($P = 0.002$) (Table 1). No significant differences were found between the groups for whole-body muscle mass ($P = 0.377$), thigh FFM volumes ($P = 0.415$), and VAT volumes ($P = 0.211$). Participants with KLGs 2 and 3 to 4, however, had significantly greater MFI ($P < 0.001$) rates, ASAT volumes ($P < 0.001$), and total abdominal

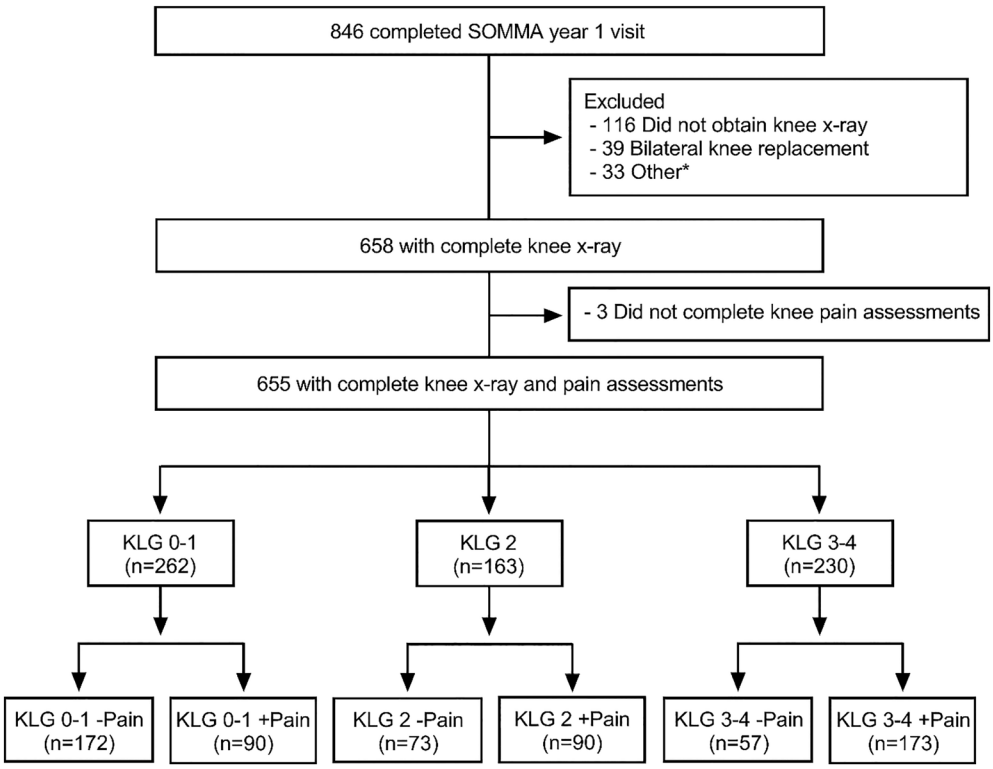

Figure 1. Study flowchart. KLG, Kellgren Lawrence Grade system for classification of osteoarthritis; -Pain, No knee pain; +Pain, Presence of knee pain. Reasons for exclusion from this study include refusal or unable to have a knee x-ray obtained (n=116), bilateral knee replacement (n=39), other (n=33), and did not complete knee pain questionnaire (n=3).

Table 1. Study participants' characteristics by Kellgren-Lawrence grade of knee osteoarthritis severity*

Characteristic	Kellgren-Lawrence grade			*P* trend
	0–1 (n = 262)	2 (n = 163)	3–4 (n = 230)	
Age, mean ± SD, y	75.6 ± 4.6	76.4 ± 5.1	76.4 ± 5.1	0.057
Female, n (%)	138 (52.7)	91 (55.8)	146 (63.5)	0.017
Race, n (%)				
White	233 (88.9)	142 (87.1)	188 (81.7)	0.032
Black	22 (8.4)	19 (11.7)	40 (17.4)	
Other	7 (2.7)	2 (1.2)	2 (0.9)	
Prescribed (Rx) medications, n (%)				
Participants taking Rx NSAIDs	15 (5.8)	14 (8.6)	32 (14.0)	0.002
Quality of life, mean ± SD				
MAT-sf score	68.9 ± 5.5	67.5 ± 5.7	65.2 ± 7.3	<0.001
Body composition, mean ± SD				
Body mass index	26.3 ± 4.1	27.7 ± 4.5	28.6 ± 4.3	<0.001
Whole body muscle mass, kg	22.3 ± 6.7	23.0 ± 6.9	21.7 ± 6.2	0.377
Height, m	1.66 ± 0.10	1.67 ± 0.10	1.65 ± 0.10	0.513
VAT volume, L	4.06 ± 2.33	4.41 ± 2.41	4.31 ± 2.03	0.211
ASAT volume, L	6.77 ± 2.85	7.50 ± 3.28	8.42 ± 3.02	<0.001
Total abdominal adipose tissue volume, L	10.83 ± 4.29	11.91 ± 4.71	12.73 ± 3.9	<0.001
Thigh fat free muscle volume, L	9.0 ± 2.3	9.3 ± 2.4	8.9 ± 2.2	0.415
Anterior thigh FFM volume, L	1.6 ± 0.5	1.6 ± 0.5	1.5 ± 0.4	0.040
Anterior thigh muscle fat infiltration, %	0.071 ± 0.019	0.075 ± 0.021	0.084 ± 0.023	<0.001
Physical activity and fitness, mean ± SD				
Steps per day	7,445 ± 3,443	7,160 ± 3,257	6,305 ± 2,955	<0.001
VO_2 peak, mL/kg/min	21.5 ± 4.8	20.5 ± 5.2	19.1 ± 4.5	<0.001
Physical performance, mean ± SD				
Gait speed, m/s	1.12 ± 0.16	1.04 ± 0.16	1.01 ± 0.19	<0.001
SPPB score	10.7 ± 1.3	10.2 ± 1.7	9.8 ± 1.9	<0.001
Knee extensor peak power, mean ± SD				
Knee extensor peak power, W	389.1 ± 170.5	379.8 ± 147.5	327.3 ± 144.1	<0.001
Peak power and thigh FFM volume, W/L	42.0 ± 10.7	40.4 ± 9.6	36.6 ± 10.4	<0.001
Mitochondrial energetics				
ATPmax, m*M*/s	0.55 ± 0.15	0.54 ± 0.16	0.53 ± 0.14	0.098
OXPHOS, pmol/(s×mg)	61.8 ± 18.2	61.2 ± 19.6	57.9 ± 18.5	0.036

* *P* trend values reflect significance from linear regression ($P < 0.05$). Total abdominal adipose tissue was calculated as VAT + ASAT. ASAT, Abdominal subcutaneous adipose tissue; ATPmax, maximal in vivo ATP production; FFM, fat-free muscle; MAT-sf score, mobility assessment tool-short form; NSAID, nonsteroidal anti-inflammatory drug; OXPHOS, maximal complex I- and II-supported oxidative phosphorylation; SPPB, Short Physical Performance Battery; VAT, visceral adipose tissue.

adipose tissue volumes ($P < 0.001$) compared to the KLG 0 to 1 group. Participants with KLG 2 and 3 or 4 also had lower self-perception of mobility ($P < 0.001$) and poorer physical performance, evidenced by slower gait speeds, lower SPPB test scores, lower leg power levels, and lower specific power levels (all $P < 0.001$). Although no significant differences were found in ATPmax between the groups ($P = 0.098$), participants with KLGs 2 and 3 to 4 had lower OXPHOS levels ($P = 0.036$) (Table 1). When stratified by sex, female (but not male) patients with KLGs 2 and 3 to 4 had greater total abdominal adipose tissue ($P < 0.001$), VAT ($P < 0.001$), and thigh FFM ($P = 0.027$) volumes; a trend toward greater whole-body muscle mass ($P = 0.057$); and lower ATPmax ($P = 0.007$) and OXPHOS ($P = 0.003$) than female patients with KLG 0 to 1 (Supplementary Tables 1 and 2).

Adjusted models of muscle health in radiographic KOA. We used multivariable linear regression models to investigate the association between KOA presence and severity and measures of muscle health in older adults (*P* trend presented), while accounting for covariates known to affect muscle parameters and/or KOA. The normal and doubtful KLG (0–1) group served as a referent group (Table 2).

After adjusting for age, sex, race, NSAID administration, site or technician, and physical activity (model 1), participants with KLGs 2 and 3 to 4 had greater thigh FFM volumes (KLG 2, mean 0.44, 95% CI 0.17–0.70; KLG 3–4, mean 0.27, 95% CI 0.02–0.51; $P = 0.027$) and MFI (KLG 2, mean 0.004%, 95% CI 0.001%–0.008%; KLG 3–4, mean 0.010%, 95% CI 0.006%–0.014%; $P < 0.001$), and slower gait speed (KLG 2, mean –0.06 m/s, 95% CI –0.09 to –0.02 m/s; KLG 3–4, mean –0.07 m/s, 95% CI –0.10 to –0.04 m/s; $P < 0.001$) than participants with KLG 0 to 1. Additionally, older adults with KLG 3 to 4 had lower peak power (mean –41.82 W, 95% CI –64.03 to –19.61 W) and specific peak power (mean –5.14 W/L, 95% CI –7.04 to –3.24 W/L) than the KLG 0 to 1 referent group. No significant group differences were observed for mitochondrial energetics after adjusting for covariates.

Table 2. Linear regression models comparing muscle parameters in older adults without and with different severity of knee osteoarthritis*

Variable	Model	Kellgren-Lawrence grade 0–1 (n = 262)	2 (n = 163), mean (95% CI)	3–4 (n = 230), mean (95% CI)	*P* trend
Muscle mass and composition					
Whole body muscle mass, kg	Unadjusted	REF	0.71 (−0.60 to 2.02)	−0.57 (−1.76 to 0.62)	0.377
	Model 1		0.95 (−0.08 to 1.98)	0.54 (−0.43 to 1.51)	0.256
	Model 2		0.60 (−0.41 to 1.60)	−0.28 (−1.24 to 0.68)	0.615
Thigh fat free muscle volume, L	Unadjusted	REF	0.24 (−0.22 to 0.70)	−0.18 (−0.60 to 0.23)	0.415
	Model 1		0.44 (0.17 to 0.70)[a]	0.27 (0.02 to 0.51)[a]	0.027
	Model 2		0.20 (−0.02 to 0.42)	0.004 (−0.20 to 0.21)	0.922
Anterior thigh fat infiltration, %	Unadjusted	REF	0.005 (0.001 to 0.009)[a]	0.013 (0.010 to 0.017)[a]	<0.001
	Model 1		0.004 (0.001 to 0.008)[a]	0.010 (0.006 to 0.014)[a]	<0.001
	Model 2		0.003 (−0.001 to 0.007)	0.008 (0.004 to 0.011)[a]	<0.001
Muscle power and physical performance					
Knee extensor peak power, W	Unadjusted	REF	−9.34 (−40.14 to 21.45)	−61.88 (−90.20 to −33.55)[a]	<0.001
	Model 1		−6.00 (−29.50 to 17.49)	−41.82 (−64.03 to −19.61)[a]	<0.001
	Model 2		−13.11 (−36.76 to 10.53)	−51.56 (−74.03 to −29.10)[a]	<0.001
Peak power and total thigh FFM volume, W/L	Unadjusted	REF	−1.63 (−3.72 to 0.47)	−5.42 (−7.33 to −3.51)[a]	<0.001
	Model 1		−1.50 (−3.52 to 0.52)	−5.14 (−7.04 to −3.24)[a]	<0.001
	Model 2		−1.68 (−3.72 to 0.37)	−5.38 (−7.31 to −3.45)[a]	<0.001
Gait speed, m/s	Unadjusted	REF	−0.08 (−0.11 to −0.05)[a]	−0.10 (−0.14 to −0.07)[a]	<0.001
	Model 1		−0.06 (−0.09 to −0.02)[a]	−0.07 (−0.10 to −0.04)[a]	<0.001
	Model 2		−0.05 (−0.08 to −0.02)[a]	−0.05 (−0.09 to −0.02)[a]	<0.001
Muscle mitochondrial energetics					
In vivo ATPmax, m*M*/s	Unadjusted	REF	−0.01 (−0.04 to 0.02)	−0.02 (−0.05 to 0.00)	0.098
	Model 1		0.01 (−0.02 to 0.04)	0.01 (−0.01 to 0.04)	0.360
	Model 2		0.01 (−0.03 to 0.04)	0.01 (−0.02 to 0.03)	0.684
Ex vivo OXPHOS, pmol/(s×mg)	Unadjusted	REF	−0.62 (−4.51 to 3.28)	−3.90 (−7.48 to −0.32)[a]	0.036
	Model 1		−0.81 (−4.39 to 2.77)	−0.49 (−3.93 to 2.96)	0.767
	Model 2		−0.26 (−3.93 to 3.41)	−0.08 (−3.64 to 3.48)	0.959

* Model 1, adjusted to age, sex, race, nonsteroidal anti-inflammatory drug administration, clinical site or technician (OXPHOS only), and physical activity. Model 2, adjusted for model 1 variables plus height and total abdominal adipose tissue volume. ATPmax, maximal in vivo ATP production; CI, confidence interval; FFM, fat-free muscle; OXPHOS, maximal complex I- and II-supported oxidative phosphorylation; REF, reference.
[a] Significantly different when compared to the Kellgren-Lawrence grade 0 to 1 REF group. Values represent betas (95% CIs). *P* values reflect significance from linear regression models ($P < 0.05$).

Considering that metabolic aspects of obesity are confounding factors when evaluating associations between knee OA and muscle health parameters, we further adjusted model 1 for height and total abdominal adipose tissue volume (model 2). The only variable that showed significantly different results when further adjusted for height and total abdominal adipose tissue volume was thigh FFM volume. We found that the higher thigh FFM volumes observed in KLG 2 and KLG 3 to 4 groups, when compared to the KLG 0 to 1 group (regression model 1), did not persist after adjustment to height and total abdominal adipose tissue volume.

Tests for interactions between knee pain and KLG were not significant at $P < 0.10$, so model stratifications were not performed. Study participants' characteristics by Kellgren-Lawrence OA severity and knee pain status can be found in Supplementary Table 3.

Sex-specific adjusted models of muscle health in radiographic KOA. Because of the distinct clinical manifestations of KOA in male and female patients, we also used multivariable linear regression models to investigate the association between KOA presence and severity and measures of muscle health in male and female patients separated (*P* trend presented; Tables 3 and 4). After adjusting for age, sex, race, NSAID administration, site or technician, physical activity, height and abdominal adiposity, both male and female patients with KLGs 3 to 4 had greater MFI levels (male patients, mean 0.010%, 95% CI 0.005%–0.015%; female patients, mean 0.006%, 95% CI 0.001%–0.011%), and lower knee extensor peak power (male patients, mean –77.26 W, 95% CI –123.02 to –31.50 W; female patients, mean –32.71 W, 95% CI –52.30 to –13.12 W) and specific power (male patients, mean –6.90 W/L, 95% CI –10.30 to –3.51 W/L; female patients, mean –4.41 W/L, 95% CI –6.70 to –2.13 W/L) than KLG 0 to 1 reference controls.

Female patients with KLG 2 had greater whole-body muscle masses (mean 1.13 kg, 95% CI 0.03–2.23 kg) and lower OXPHOS levels (mean –4.77 pmol/[s×mg], 95% CI –9.20 to –0.33 pmol/[s×mg]) than female patients with KLG 0 to 1, whereas no such differences were observed in male patients.

Table 3. Linear regression models comparing muscle parameters in older female patients with different severity of knee osteoarthritis and older female patients without knee osteoarthritis*

Variable	Model	Kellgren-Lawrence grade 0–1 (n = 138)	Kellgren-Lawrence grade 2 (n = 91), mean (95% CI)	Kellgren-Lawrence grade 3–4 (n = 146), mean (95% CI)	*P* trend
Muscle mass and composition					
Whole-body muscle mass, kg	Unadjusted	REF	1.27 (0.12 to 2.41)[a]	0.99 (−0.01 to 1.99)	0.057
	Model 1		1.39 (0.25 to 2.53)[a]	0.91 (−0.12 to 1.94)	0.093
	Model 2		1.13 (0.03 to 2.23)[a]	0.08 (−0.93 to 1.09)	0.915
Thigh fat free muscle volume, L	Unadjusted	REF	0.35 (0.06 to 0.64)[a]	0.29 (0.04 to 0.55)[a]	0.027
	Model 1		0.39 (0.10 to 0.68)[a]	0.28 (0.02 to 0.55)[a]	0.038
	Model 2		0.15 (−0.09 to 0.38)	0.01 (−0.20 to 0.23)	0.943
Anterior thigh fat infiltration, %	Unadjusted	REF	0.004 (−0.002 to 0.009)	0.011 (0.007 to 0.016)[a]	<0.001
	Model 1		0.001 (−0.005 to 0.007)	0.008 (0.003 to 0.013)[a]	0.003
	Model 2		0.001 (−0.005 to 0.006)	0.006 (0.001 to 0.011)[a]	0.026
Muscle power and physical performance					
Knee extensor peak power, W	Unadjusted	REF	4.85 (−17.82 to 27.53)	−23.32 (−43.45 to −3.19)	0.024
	Model 1		13.45 (−9.34 to 36.25)	−20.02 (−40.51 to 0.47)	0.056
	Model 2		1.21 (−20.33 to 22.74)	−32.71 (−52.30 to −13.12)[a]	0.001
Peak power/total thigh FFM volume, W/L	Unadjusted	REF	−0.96 (−3.44 to 1.52)	−3.93 (−6.13 to −1.73)[a]	<0.001
	Model 1		−0.10 (−2.59 to 2.40)	−3.75 (−6.00 to −1.49)[a]	0.001
	Model 2		−0.57 (−3.08 to 1.94)	−4.41 (−6.70 to −2.13)[a]	<0.001
Gait speed, m/s	Unadjusted	REF	−0.06 (−0.11 to −0.02)[a]	−0.10 (−0.14 to −0.06)[a]	<0.001
	Model 1		−0.01 (−0.06 to 0.03)	−0.06 (−0.09 to −0.02)[a]	0.006
	Model 2		−0.01 (−0.06 to 0.03)	−0.03 (−0.07 to 0.01)	0.115
Muscle mitochondrial energetics					
In vivo ATPmax, m*M*/s	Unadjusted	REF	−0.04 (−0.08 to −0.002)[a]	−0.05 (−0.08 to −0.01)[a]	0.007
	Model 1		−0.01 (−0.05 to 0.02)	−0.01 (−0.04 to 0.02)	0.506
	Model 2		−0.01 (−0.05 to 0.03)	−0.01 (−0.05 to 0.02)	0.476
Ex vivo OXPHOS, pmol/(s×mg)	Unadjusted	REF	−6.37 (−10.85 to −1.90)[a]	−6.07 (−10.05 to −2.10)[a]	0.003
	Model 1		−4.69 (−9.02 to −0.35)[a]	−2.31 (−6.33 to 1.70)	0.243
	Model 2		−4.77 (−9.20 to −0.33)[a]	−2.40 (−6.57 to 1.77)	0.244

* Model 1, adjusted to age, sex, race, nonsteroidal anti-inflammatory drug administration, clinical site or technician (OXPHOS only), and physical activity. Model 2, adjusted for model 1 variables plus height and total abdominal adipose tissue volume. ATPmax, maximal in vivo ATP production; CI, confidence interval; FFM, fat-free muscle; OXPHOS, maximal complex I- and II-supported oxidative phosphorylation; REF, reference.
[a] Significantly different when compared to the Kellgren-Lawrence grade 0 to 1 REF group. Values represent betas (95% CIs). *P* values reflect significance from linear regression models ($P < 0.05$).

However, male (but not female) patients with KOA showed lower gait speeds (KLG 2, mean –0.08 m/s, 95% CI – 0.13 to –0.03 m/s; KLG 3–4, mean –0.08 m/s, 95% CI –0.13 to –0.03 m/s) when compared to male patients with KLG 0 to 1.

We found no interaction between KOA groups and pain for all outcomes, except for OXPHOS, in which pain does seem to make a difference in male patients only (referent group: KLG 0–1 and no pain; KLG 0–1 and pain: mean 10.43 pmol/[s×mg], 2.45–18.42 pmol/[s×mg]; KLG 2 and no pain, 12.83 pmol/[s×mg], 95% CI 4.41–21.26 pmol/[s×mg]). Descriptive characteristics of male and female patients by KLG for OA severity and knee pain status can be found in Supplementary Tables 4 and 5.

Associations between cellular characteristics and muscle volume and power in KOA. We investigated the association between two muscle intrinsic characteristics (MFI and OXPHOS) and muscle volume and power among those with KOA (KLGs 2 and 3–4). Bivariate correlation analyses showed that MFI was negatively correlated with anterior thigh FFM volume (r = –0.345, $P < 0.001$), peak power (r = –0.398, $P < 0.001$), and anterior thigh specific power (r = –0.271, $P < 0.001$) in participants with KOA (Figure 2). OXPHOS was positively associated with anterior thigh FFM volume (r = 0.382, $P < 0.001$), leg power (r = 0.408, $P < 0.001$), and specific power (r = 0.214, $P < 0.001$).

DISCUSSION

Muscle health, including muscle composition, power, and energetics, is associated with the presence and severity of KOA in older adults, and some of these associations are different in male and female patients. Additionally, our results suggest that associations between muscle health and KOA are independent of knee pain and that muscle cellular characteristics, including MFI and OXPHOS, are associated with thigh FFM volume, leg power, and specific power in older adults with KOA.

In this study, we assigned participants to one of three groups according to the presence and severity of KOA. We found greater MFI and lower leg power and specific power only in individuals

Table 4. Linear regression models comparing muscle parameters in older male patients with different severity of knee osteoarthritis and older male patients without knee osteoarthritis*

Variable	Model	Kellgren-Lawrence grade 0–1 (n = 124)	Kellgren-Lawrence grade 2 (n = 72), mean (95% CI)	Kellgren-Lawrence grade 3–4 (n = 84), mean (95% CI)	*P* trend
Muscle mass and composition					
Whole body muscle mass, kg	Unadjusted	REF	0.48 (−1.32 to 2.29)	−0.46 (−2.20 to 1.29)	0.670
	Model 1		0.35 (−1.48 to 2.18)	0.09 (−1.74 to 1.91)	0.898
	Model 2		0.04 (−1.77 to 1.85)	−0.73 (−2.53 to 1.07)	0.453
Thigh fat free muscle volume, L	Unadjusted	REF	0.51 (0.04 to 0.98)[a]	0.15 (−0.29 to 0.59)	0.384
	Model 1		0.54 (0.07 to 1.02)[a]	0.32 (−0.14 to 0.78)	0.1294
	Model 2		0.34 (−0.07 to 0.75)	0.06 (−0.34 to 0.45)	0.664
Anterior thigh fat infiltration, %	Unadjusted	REF	0.004 (−0.001 to 0.010)	0.013 (0.007 to 0.018)[a]	<0.001
	Model 1		0.006 (0.001 to 0.013)[a]	0.012 (0.006 to 0.018)[a]	<0.001
	Model 2		0.004 (−0.001 to 0.010)	0.010 (0.005 to 0.015)[a]	<0.001
Muscle power and physical performance					
Knee extensor peak power, W	Unadjusted	REF	−16.23 (−60.79 to 28.33)	−64.57 (−108.04 to −21.10)[a]	0.005
	Model 1		−27.91 (−71.86 to 16.04)	−70.58 (−115.23 to −25.93)[a]	0.002
	Model 2		−28.80 (−74.22 to 16.62)	−77.26 (−123.02 to −31.50)[a]	0.001
Peak power/total thigh FFM volume, W/L	Unadjusted	REF	−1.96 (−5.30 to 1.38)	−6.09 (−9.30 to −2.89)[a]	<0.001
	Model 1		−3.09 (−6.47 to 0.28)	−7.04 (−10.40 to −3.69)[a]	<0.001
	Model 2		−3.00 (−6.41 to 0.41)	−6.90 (−10.30 to −3.51)[a]	<0.001
Gait speed, m/s	Unadjusted	REF	−0.09 (−0.14 to −0.05)[a]	−0.09 (−0.14 to −0.05)[a]	<0.001
	Model 1		−0.09 (−0.14 to −0.05)[a]	−0.09 (−0.14 to −0.04)[a]	<0.001
	Model 2		−0.08 (−0.13 to −0.03)[a]	−0.08 (−0.13 to −0.03)[a]	<0.001
Muscle mitochondrial energetics					
In vivo ATPmax, m*M*/s	Unadjusted	REF	0.03 (−0.02 to 0.08)	0.02 (−0.03 to 0.06)	0.476
	Model 1		0.02 (−0.03 to 0.08)	0.04 (−0.01 to 0.09)	0.088
	Model 2		0.02 (−0.03 to 0.07)	0.03 (−0.02 to 0.08)	0.233
Ex vivo OXPHOS, pmol/(s×mg)	Unadjusted	REF	5.59 (−0.41 to 11.59)	0.32 (−5.46 to 6.10)	0.772
	Model 1		3.38 (−2.67 to 9.43)	1.53 (−4.54 to 7.61)	0.569
	Model 2		4.45 (−1.73 to 10.62)	2.28 (−3.92 to 8.49)	0.415

* Model 1, adjusted to age, sex, race, nonsteroidal anti-inflammatory drug, clinical site or technician (OXPHOS only), and physical activity. Model 2, adjusted for model 1 variables plus height and total abdominal adipose tissue volume. ATPmax, maximal in vivo ATP production; CI, confidence interval; FFM, fat-free muscle; OXPHOS, maximal complex I- and II-supported oxidative phosphorylation; REF, reference.
[a] Significantly different when compared to the Kellgren-Lawrence grade 0 to 1 REF group. Values represent betas (95% CIs). *P* values reflect significance from linear regression models ($P < 0.05$).

with moderate to severe KOA, supporting the hypothesis that not only presence but severity of KOA influences the association between KOA and muscle health. These results may suggest that worse muscle health may lead to worse severity of KOA, or that advanced KOA may lead to changes in muscle characteristics. The cross-sectional nature of our study prevents us from better understanding the association between the two, but future longitudinal studies should be conducted to guide KOA prevention and treatment.

Muscle cellular and molecular adaptations have been reported in symptomatic and radiographic KOA, including changes in myofiber type distribution and cross-sectional area, greater extracellular matrix content, decreased single muscle fiber force production, and slower myosin-actin cross-bridge kinetics.[8] More recently, it has been shown that intrinsic muscle characteristics play a role on muscle strength in KOA.[9] We found that both older male and female patients with KOA had significantly higher MFI. Interestingly, the greater MFI and lower leg power in older adults with moderate to severe KOA persisted even after adjusting for abdominal adiposity, a measure of metabolic syndrome. These findings suggest that differences in muscle characteristics between study participants with and without KOA are independent of obesity and metabolic syndrome and are likely characteristics of KOA. The greater MFI and lower leg power in individuals with advanced KOA were seen in both male and female patients. Interestingly, the unadjusted comparisons showed very distinct body composition characteristics in male and female patients in our study population, with female (but not male) patients with KOA having greater VAT, total abdominal adiposity, and thigh FFM volume. Our findings suggest that greater MFI and lower leg power are indeed characteristics of moderate to severe KOA, independent of sex or body adiposity.

In this study, we used knee extensor peak power (the product of the force and velocity of muscle contraction) rather than muscle strength because this variable is a better predictor of physical function in older adults. In our regression model 2, older adults with moderate to severe KOA had reduced leg power,

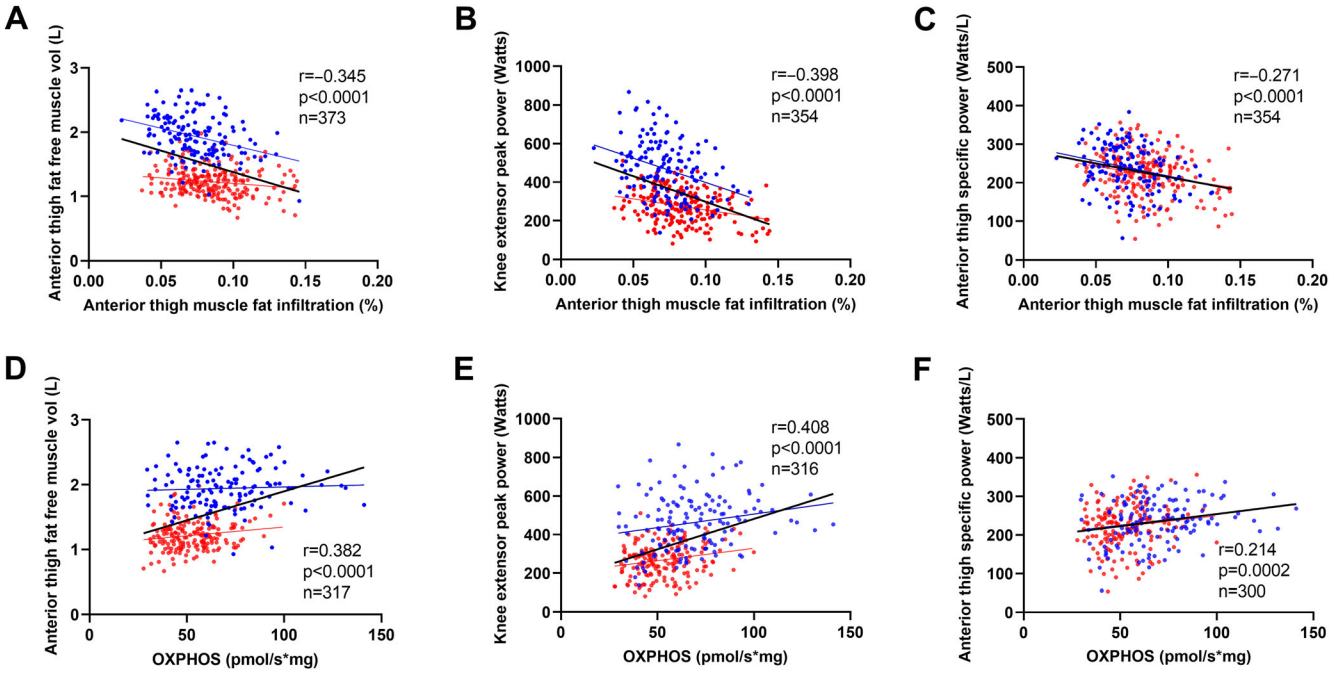

Figure 2. Associations between muscle intrinsic characteristics (anterior thigh muscle fat infiltration and mitochondrial respiration) and muscle volume, peak power, and specific power in study participants with knee osteoarthritis. (A–C) Association between anterior thigh muscle fat infiltration assessed by magnetic resonance imaging with (A) anterior thigh fat free muscle volume, (B) knee extensor peak power, and (C) anterior thigh specific power (knee extensor peak power/thigh fat free muscle volume, specific power). (D–F) Association between OXPHOS assessed on muscle biopsy samples and (D) anterior thigh fat free muscle volume, (E) knee extensor peak power, and (F) anterior thigh specific power (knee extensor peak power or thigh fat free muscle volume and specific power). Results represent simple linear regressions for male (blue dots and line) and female (red dots and line) patients. $P < 0.05$. OXPHOS, maximal complex I- and II-supported oxidative phosphorylation. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.42953/abstract.

despite greater thigh FFM volume. Our leg power findings align with previous studies that have reported reduced muscle strength[8] and preserved or increased muscle mass in individuals with KOA.[12] Although muscle strength and mass are significantly associated,[6] declines in muscle strength with aging are known to be greater than declines in muscle mass.[36] Our findings suggest that KOA may affect muscle parameters in a similar manner as aging. The association between leg muscle mass and quadriceps strength or power is also reported to differ by KOA severity, with the association weakening with increased severity.[37] The preserved or increased muscle volume that we observe in older adults with KOA is likely attributed to obesity because individuals with obesity have higher muscle mass as part of a higher total body mass.[38]

In the current study, older adults with moderate to severe KOA also had lower specific power (peak power adjusted for thigh FFM volume). The study by Conroy et al[12] showed that compared to age-matched controls, older adults with radiographic KOA had significantly lower thigh torque adjusted for thigh area, indicating poor muscle quality. Similarly, the study by Slemenda et al[31] reported that reduced leg strength relative to thigh muscle mass was associated with KOA. Our findings complement these studies using more advanced and accurate measures of whole-body muscle mass (D_3Cr dilution method) and thigh FFM volume (MRI). We also examined whether the reduced specific peak power observed in those with KOA was concomitant to reduced physical performance and found that older adults with KOA had lower gait speeds and SPPB test scores. Collectively, our findings suggest that factors other than muscle size play a role on the decreased muscle power observed in older adults with KOA, such as neuromuscular activation, biomechanics of the knee joint, knee pain, and intrinsic muscle characteristics.

Increased adiposity and decreased physical activity are known to be associated with reduced muscle mitochondrial energetics.[15,17] We used state-of-the-art methodology to investigate mitochondrial energetics and found that in vivo ATP production and oxidative phosphorylation measured in muscle biopsy samples were significantly lower in older female (but not male) patients with KOA, when compared to controls without KOA. However, the differences were not significant after adjusting for covariates. We hypothesize that the lower mitochondrial energetics in female patients with KOA may result from reduced physical activity, a major determinant of mitochondrial function.[17] Few studies have reported mitochondrial energetics in individuals with KOA.[11,39] The study by Fink et al[10] reported sex-specific differences in subsarcolemmal mitochondria content with lower values in female patients with KOA. This may be the first study investigating

mitochondrial function, rather than content or structure, in older adults with KOA.

Importantly, both MFI and OXPHOS were associated with leg power and specific power in study participants with KOA, supporting the premise that muscle intrinsic characteristics may influence muscle function of older adults with KOA. Although the association between OXPHOS and leg power has been reported in the complete SOMMA cohort, which includes study participants with and without KOA,[24] we confirmed OXPHOS is associated with leg power in study participants with KOA and demonstrated that OXPHOS is also positively associated with muscle volume. We also investigated the influence of knee pain on muscle characteristics of study participants with and without KOA and found no significant associations. The study by Muraki et al[40] found a significant association between quadriceps muscle strength and knee pain, independent of radiographic KOA.

Strengths of this study include a large population of older adults with and without KOA and a comprehensive investigation of whole body and muscle function and composition. This is also the first study performing a comprehensive in vivo and ex vivo assessment of muscle mitochondrial energetics. A limitation of this study includes the study cross-sectional design; therefore, causal relationships between muscle composition, power, and mitochondrial energetics and KOA cannot be established. We also acknowledge that our study only collected pain medications that were prescribed by a health care provider; therefore, we may have underestimated pain medication intake because over-the-counter medications were not recorded, and this may have influenced participants' physical activity. In addition, our knee radiographs were obtained at the first follow-up visit, whereas the muscle composition and mitochondrial assessments were obtained at the baseline visit. In this report, baseline data were used for everything except the knee radiographs because analyses between baseline and year-one data demonstrated no differences in outcome measures. Because 86% of our study participants self-reported as being non-Hispanic White, our study may not be generalized to other races and ethnicities.

In summary, muscle health is associated with the presence and severity of KOA and differs between male and female patients with KOA. Although muscle composition and power are lower in both male and female patients with KOA regardless of pain status, mitochondrial energetics is reduced only in female patients. Future studies that investigate muscle cellular characteristics of older adults with KOA will provide more insights into the muscle intrinsic characteristics that influence mass, power, and performance in older adults with KOA and may guide therapy.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Lane confirms that all authors have provided the final approval of the version to be published, and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Helsinki Declaration requirements.

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