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Thigh muscle features in female patients with severe knee osteoarthritis: a cross-sectional study

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Abstract

Background Muscle function deterioration in female patients with severe knee osteoarthritis (KOA) is linked to alterations in muscle morphology, composition, and mechanical properties. This study evaluates thigh muscle features in female patients with severe KOA and explores correlations with knee joint function.

Methods Ultrasound and shear wave elastography measured physiological cross-sectional area (PCSA), echo intensity (EI), and shear modulus (G) in the rectus femoris (RF), vastus lateralis (VL), vastus medialis (VM), biceps femoris long head (BFL), and semitendinosus (ST) of 24 KOA patients and 24 controls. EI indicates intramuscular fat, while G reflects stiffness. Muscle characteristics were compared between groups, and correlations with knee function scores (WOMAC, KSS, HSS) were analyzed.

Results In patients, the symptomatic side displayed reduced PCSA for RF, VL, VM, BFL, and ST (15.85 cm^2, 28.18 cm^2, 21.53 cm^2, 11.67 cm^2, 6.59 cm^2 respectively) vs. controls (19 cm^2, 36.32 cm^2, 23.37 cm^2, 14.15 cm^2, 7.12 cm^2 respectively). EI was elevated (128.95, 121.12, 105.72, 90.52, 93.15) vs. controls (100.39, 93.97, 88.14, 77.69, 78.73), and G values (9.48 kPa, 7.88 kPa, 6.9 kPa, 7.2 kPa, 9.03 kPa) was higher than controls (8.85 kPa, 5.28 kPa, 5.98 kPa, 6.58 kPa, 6.73 kPa). BFL`s G, ST`s G, and VM`s EI, negatively correlated with knee function, whereas BFL`s PCSA positively correlated. The variable importance of BFL's PCSA and G ranked at the top in all scores.

Conclusions Compared to controls, PCSAs in muscles on both sides of KOA patients were lowered by up to 22%, indicative of muscle loss and diminished strength. The G value is 20.65% higher, suggesting poor flexibility and elevated passive tension. EI in muscles on both sides of KOA patients was greater, reaching up to 23.88%, possibly reducing contractile components and muscle force. G, PCSA, and EI are closely correlated with function scores, and PCSA and G of BFL are the most significant predictors of knee function. These results may help explain muscle dysfunction in KOA patients.

Clinical trial number Not applicable.

Keywords Knee osteoarthritis, Ultrasonography, Physiological cross-sectional area, Echo intensity, Shear modulus

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Background

Knee osteoarthritis (KOA) is a prevalent chronic degenerative disease characterized by the degradation of joint cartilage, subchondral bone sclerosis, and osteophyte formation, ultimately leading to knee joint deformity and disability [1]. KOA is recognized as one of the leading causes of disability globally [2], with a notably higher prevalence among females, who are at 2.6 times greater risk than males [3]. Declines in muscle function are common in female KOA patients [4], and muscle dysfunction has been identified as a critical risk factor influencing the onset and progression of KOA [5]. Muscle function is closely linked to a variety of muscle characteristics, including morphology, composition, and mechanical properties [6, 7]. The muscular dysfunction observed in female KOA patients may be attributed to changes in these muscle characteristics [8], which often result from complex interactions among them [9]. However, the specific changes in some muscle characteristics and their interrelationships in female patients with severe KOA have not been thoroughly investigated.

Female patients with KOA commonly experience thigh muscle atrophy, with significant changes observed in key morphological parameters, such as muscle cross-sectional area (CSA), muscle thickness, and pennation angle [10, 11]. Alterations in muscle morphology have a substantial impact on muscle strength, and changes in muscle strength may affect joint load distribution, potentially accelerating the progression of KOA [12]. Therefore, it is crucial to investigate changes in muscle morphology and structure in these patients. Previous studies have frequently utilized muscle CSA to assess muscle atrophy [11], but muscle atrophy are also symptomatic by other critical structural features such as pennation angle and fascicle length [13]. Moreover, previous studies found that the relationship between muscle CSA and KOA score is not as strong as that between muscle mass and KOA score [8]. To address it, physiological cross-sectional area (PCSA) may provide a more appropriate metric for evaluating muscle mass. The computation of PCSA also encompasses critical morphological structural data such as muscle volume, pennation angle, and fascicle length [14], potentially offering a more comprehensive reflection of muscle loss. Furthermore, PCSA is also a fundamental parameter for estimating muscle force [14, 15], which may more accurately reflect the impact of lower limb muscle atrophy on muscle weakness. Despite its evident importance, there is currently a lack of research investigating changes in the PCSA of thigh muscles in KOA patients, and no studies have explored the direct and independent effects of thigh muscle PCSA on KOA symptoms.

Muscle mechanical properties are equally critical for functional performance, with stiffness serving as an indicator of the force generated during muscle contraction [16]. Increased passive stiffness in the thigh muscles may reduce muscle compliance, impede knee flexion, and contribute to joint rigidity [17]. Previous research has linked elevated quadriceps stiffness with a higher risk of KOA [18]. The shear modulus (G) is a quantitative measure of muscle stiffness [17]. Although several studies have quantified the G values of the thigh muscles in KOA patients [19, 20], few specifically examine female subjects. Gender differences influence the degree of muscle stiffness changes [21], but whether similar gender-based differences exist in the mechanical properties of thigh muscles in KOA patients remains unclear. Therefore, further research focusing on the biomechanical changes in the thigh muscles of female KOA patients is highly desired.

Intramuscular fat, as assessed by echo intensity (EI) through ultrasound grayscale analysis [22], is another critical factor for evaluating muscle function. Healthy muscle tissue is normally echolucent or dark, with a hypoechoic component representing the muscle fibers and a hyperechoic component representing the connective scaffold [23]. When muscle tissue undergoes pathological changes such as fat infiltration, these alterations establish multiple new acoustic reflection planes within the muscle, leading to the diseased muscle becoming progressively more echogenic [24]. Given the strong correlations observed between the MRI-measured percentage of intramuscular fat and muscle EI [25], a higher EI can serve as a reliable indicator of greater intramuscular fat accumulation. Numerous studies have utilized ultrasound imaging techniques, in conjunction with EI measurements, to delve into the condition of muscle fat infiltration in KOA patients as well as in the elderly [9, 22]. Individuals with KOA exhibit a higher degree of fat infiltration within the thigh muscles compared to those without KOA [26]. The elevated intramuscular fat infiltration is tightly associated with diminished muscle strength and functional decrements [27], which is a phenomenon particularly pronounced in female patients with knee osteoarthritis [28]. Previous studies often isolated changes in muscle quality and quantity, proposing that each factor independently affects muscle strength [29]. However, alterations in muscle composition, particularly increased intramuscular fat, may remodel muscle morphology and mechanical properties, such as the pennation angle [9] and muscle stiffness [30], thereby reducing muscle fiber stress and compliance, ultimately limiting force production. It remains unclear whether elevated intramuscular fat content in KOA patients mediates changes in other muscle characteristics, such as morphological structure and mechanical properties.

Alterations in thigh muscle characteristics among KOA patients not only compromise muscle functionality,

but also worsen KOA symptoms, impose restrictions on daily activities, and accelerate the progression of the disease. Physical function scores reflect the severity of functional impairment and symptoms and can be used to explore the impact of muscle characteristics on functional outcomes in KOA. The Knee Society Score (KSS), the American Hospital for Special Surgery (HSS) scoring system, and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), are closely associated with the muscle function of KOA patients [31, 32]. However, the extent to which these muscle changes impact overall physical function scores, as well as which muscle characteristics are most significantly symptomatic, requires further investigation.

Ultrasound (US) technology has gained prominence in the evaluation of muscle structural parameters due to its high accuracy and convenience. US allows for real-time visualization of muscle anatomy, with measurements closely correlated to muscle structural data obtained via magnetic resonance imaging (MRI) [33]. Shear wave elastography (SWE), an innovative technique in ultrasound imaging, provides quantitative data on the mechanical properties of in vivo soft tissues [34], encompassing measures such as shear modulus. Owing to its high sensitivity and specificity, SWE is gaining attention as a clinical tool for the assessment of soft tissue rigidity.

Understanding muscle characteristics is essential for elucidating the mechanisms behind muscle dysfunction, which is crucial for developing strategies to prevent muscle deterioration and improve physical function. The objectives of this study are: (1) to assess the thigh muscle characteristics of female KOA patients using ultrasound imaging and shear wave elastography, and to compare these characteristics with those of healthy controls; (2) to investigate the interplay between muscle characteristics and to assess the correlations between muscle characteristics and knee joint function scores in female patients with severe KOA.

Methods

Participants

Twenty-four female patients with KOA were recruited (Table 1). Inclusion criteria were as follows: (1) Age range 55–70 years [35]; (2) BMI ≤ 28 kg/m^2 [36]; (3) Meeting the diagnostic criteria of KOA by the American College of Rheumatology [37]; (4) Kellgren-Lawrence (K-L) grade III-IV [38]; (5) Ability to walk independently. Exclusion criteria were: (1) Concurrent neurological diseases such as stroke, Parkinson's disease, etc.; (2) Muscle disorders such as severe myasthenia gravis, progressive malnutrition, periodic paralysis, etc.; (3) History of major trauma, surgery; (4) Other inflammatory arthritis conditions; (5) Patients with bilateral KOA. All patients with KOA in our study have had the condition for a duration of more than three years. Twenty-four healthy females were recruited as control subjects, with no history of musculoskeletal or neurological disorders. The right leg of all healthy individuals was uniformly measured to ensure consistency within the control group. No significant differences in age, height, weight, or BMI were observed between the healthy controls and KOA groups (Table 1). Ethical approval for this study was granted by Capital Medical University(2022SY122). During the conduct of this research, we adhered to the ethical guidelines set forth in the Declaration of Helsinki. Written informed consent was obtained from all participants.

Ultrasound measurements

The onset and progression of KOA are closely linked to degenerative changes in the quadriceps and hamstrings [29], which significantly impair physical performance [39]. Assessing these muscle changes is essential

Table 1 Participant characteristics

	KOA group($n=24$)	Healthy group($n=24$)	t (95% CI)	*P*
Age (y)	67.21 (1.82)	67. 75 (3.63)	0.654 (-1.141 ~ 2.225)	0.527
Height (cm)	159.00 (7.71)	157.21 (7.03)	-0.842 (-6.077 ~ 2.494)	0.404
Weight (kg)	65.44 (5.58)	67.42 (5.20)	1.272 (-1.155 ~ 5.114)	0.210
BMI (kg/m^2)	26.05 (3.50)	27.48 (3.71)	1.363 (-0.677 ~ 3.518)	0.179
KL grade	III/IV (6/18)	—	—	—
WOMAC pain	36.44 (2.67)	—	—	—
WOMAC stiffness	15.84 (1.73)	—	—	—
WOMAC physical function	66.08 (9.04)	—	—	—
WOMAC total	117.337 (12.27)	—	—	—
KSS Symptom	33.22 (2.45)	—	—	—
KSS Function	53.59 (8.12)	—	—	—
KSS total	86.81 (10.01)	—	—	—
HSS	50.44 (5.70)	—	—	—

Values are presented as mean (standard deviation)

KOA Knee osteoarthritis, BMI Body mass index, KL Kellgren-Lawrence, WOMAC Western Ontario and McMaster Universities Arthritis Index, KSS American Knee Society Score, HSS Hospital for Special Surgery, CI Confidence intervals, P p-value

for understanding muscle dysfunction mechanisms and developing strategies to prevent degeneration and enhance function [40]. Due to the limitations of ultrasound techniques in terms of imaging depth and resolution [41–43], as well as the varying contributions of individual muscles within the quadriceps and hamstrings to knee function [44, 45], we selected the rectus femoris (RF), vastus lateralis (VL), vastus medialis (VM), biceps femoris long head (BFL), and semitendinosus (ST) for ultrasound data collection. These muscles were measured bilaterally in patients and unilaterally in healthy controls using the Aixplorer real-time shear wave elastography ultrasound diagnostic instrument (Aixplorer; SuperSonic Imagine, Aix-en-Provence, France) with an L10-2 probe. Bony structures around the knee joint were used as anatomical landmarks in the ultrasound images to ensure consistency in measurement locations across all participants [17] (Table 2).

To ensure relaxed measurement conditions, subjects refrained from vigorous exercise before data collection and rested for 5 min prior to testing. While lying supine and fully relaxed, the room temperature was kept at a constant 25 °C. Sufficient gel was applied to facilitate optimal probe-to-skin contact, with the examiner careful to avoid excessive tissue pressure. An initial two-dimensional ultrasound was conducted to evaluate muscle morphology, followed by the activation of elastography mode. Transverse ultrasound scans determined muscle cross-sectional area and thickness, and subsequent longitudinal scans were used to quantify the pennation angle and shear modulus.

Muscle CSA was quantified using panoramic imaging techniques, wherein the probe was kept perpendicular to the skin surface and glided slowly and continuously along the skin to encapsulate the full muscle cross-Sect. [46] (Fig. 1). Muscle thickness (MT) was defined as the distance between two strong echo bands parallel to each other in the ultrasound image, representing the distance between the superficial and deep fascial coats [29, 47].

Table 2 Sites of muscle measurement using ultrasonography

Muscle	Measurement site
RF	lower one-third of the line connecting the anterior superior iliac spine and the upper edge of the patella
VL	lower fifth of the line connecting the greater trochanter of the femur and the medial condyle of the femur
VM	lower one-third of the line connecting the greater trochanter of the femur and the lateral condyle of the femur
BFL	the lower third of the line connecting the ischial tuberosity and the lateral popliteal fossa
ST	the lower third of the line connecting the ischial tuberosity and the medial popliteal fossa

RF Rectus Femoris, VM Vastus Medialis, VL Vastus Lateralis, BFL Biceps Femoris long head, ST Semitendinosus

Pennation angle (α) refers to the angle formed between the direction of muscle bundles and the deep fascia coats, while muscle fascicle length (L_f) indicates the line connecting the intersections of muscle bundles with the superficial and deep fascia coats, calculated according to the formula: $L_f = MT/\sin\alpha$.

Muscle elasticity parameters were measured within a range of 0–80 kPa, using a fixed-size rectangular box selected on the muscle. Q-Box (diameter 5 mm) was used to measure the shear modulus of the muscle. Three measurements were taken at the same location, with at least a 3-second interval between each ultrasound image acquisition. All ultrasound images were obtained by a physician with five years of experience in musculoskeletal ultrasound imaging.

Physiological cross-sectional area calculation

Utilizing regression equations that correlate muscle CSA with volume facilitates the computation of individual muscle volumes [48, 49]. Thigh length, defined as the distance from the greater trochanter to the knee joint space, was measured with participants in a standing, relaxed position. The distal end of the thigh, located at the knee joint space, was designated as the 0% mark. In healthy individuals, the muscle CSAs of the quadriceps were measured at 50% of thigh length, while for the hamstring muscles, measurements were taken at 40% of thigh length [48]. For KOA patients, measurements were taken at 40% of thigh length for both quadriceps and hamstring muscles [49]. Muscle PCSAs were calculated using the following formula [50], with intercept and slope values referenced from Table 3 [48, 49]:

$$MV_H = FL \times (CSA \times Slope_H + Intercept_H) \quad (1)$$

[48].

$$MV_P = FL \times CSA \times Slope_P + Intercept_P \quad (2)$$

[49].

$$PCSA = MV \times \cos\alpha / L_f \quad (3)$$

[50].

MV_Hrepresents muscle volume in healthy controls, MV_P represents muscle volume in KOA group, FL is thigh length, CSA is the anatomical cross-sectional area, $PCSA$ is the physiological cross-sectional area, MV is single muscle volume, α represents pennation angle, L_f represents muscle fascicle length.

Echo intensity

Muscle EI values were calculated from ultrasound images obtained from muscle thickness measurements, stored

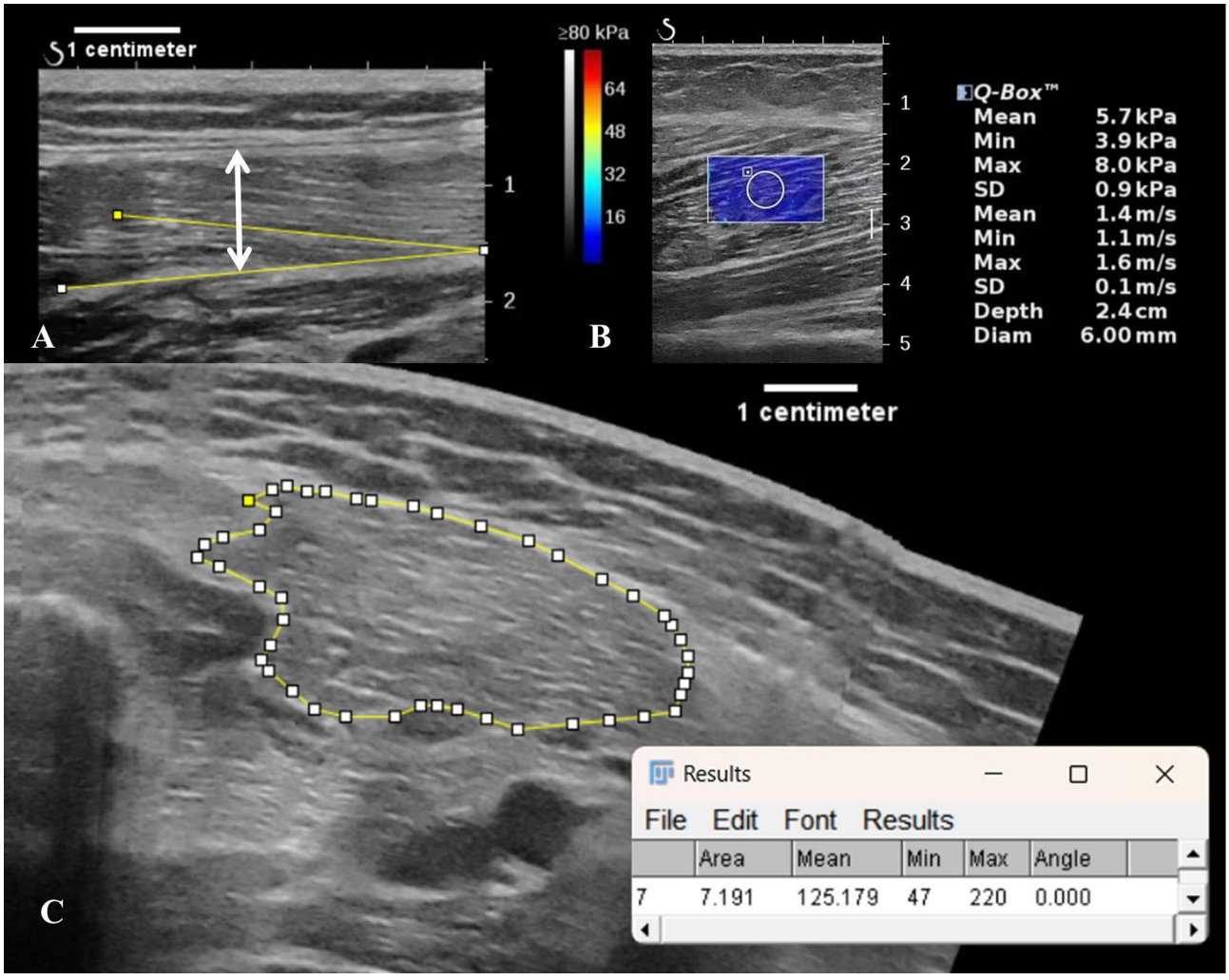

Fig. 1 Sonographic measurement for thigh muscle features. **A**: illustrates the process of measuring muscle thickness and pennation angle; **B**: depicts the procedure for measuring muscle shear modulus; **C**: represents the process of measuring muscle cross-sectional area and echo intensity

Table 3 The intercept and slope of the muscle volume prediction eqs. [48, 49]

Muscle	Healthy group		KOA group	
	Intercept	Slope	Intercept	Slope
RF	0.749	0.717	17.9	0.56
VL	0.581	0.529	8.1	0.54
VM	1.329	0.556	32.3	0.44
BFL	0.211	0.326	5	0.31
ST	0.687	0.431	18.2	0.41

RF Rectus Femoris, VM Vastus Medialis, VL Vastus Lateralis, BFL Biceps Femoris long head, ST Semitendinosus

in DICOM format. EI was defined as the average gray-scale value (0-255) within the selected region, analyzed using standard histogram functions in ImageJ software (National Institutes of Health, Bethesda, MD, USA) [51].

Knee joint scores

The WOMAC score, the KSS score, and the HSS score were used to assess the knee joint functions in the daily activities of KOA patients. The WOMAC score is a self-administered questionnaire comprising 24 items that are categorized into three subscales: pain, stiffness, and physical function [52].As the WOMAC score increases, it reflects a worsening of pain, stiffness, and functional limitations associated with KOA. The KSS score is structured around two sections: knee joint, which includes assessments of pain, range of motion, and stability, and function. The HSS scoring system is frequently used for both preoperative and postoperative evaluations of knee joint function, encompassing six domains, including pain and muscle strength. A higher score on both the KSS and HSS scales signifies better knee function and less disease severity [31, 32].

Data analysis

Utilizing the preliminary elastic data from a pilot study for sample size determination, our analysis indicates that a sample size of 17 participants per group will suffice to achieve a statistical power exceeding 0.8. The Shapiro-Wilk test confirmed the normality of data across variables. Normally distributed data are presented as mean ± SD; non-normally distributed data as median (IQR). Paired t-tests were applied to assess differences between symptomatic and asymptomatic sides within the same group, while independent t-tests were used to compare patient and control groups. For non-normally distributed data, the Kruskal-Wallis test was employed to compare groups, followed by post-hoc analysis with the Benjamini-Hochberg correction to mitigate the risk of Type I error resulting from multiple comparisons and determine the significance of pairwise differences between groups. Pearson or Spearman correlations were utilized to examine the relationships between muscle parameters and knee scores, depending on the normality of the variables. Linear and stepwise regressions were conducted to assess the impact of muscle parameters on knee scores. Partial least squares (PLS) regression was employed to identify critical muscle attributes that influence physical function. All statistical analyses were performed using SPSS 26.0 with a significance level of α =0.05.

Results

Muscle characteristics

The reliability statistics for each muscle parameter are summarized in Table 4. There was no systematic variability observed for each parameter across muscles during the trial ($p = 0.211–0.995$). Reliability analysis indicated a high degree of consistency in the measurements of each parameter for the respective muscles, with ICC values greater than 0.971 and SEM% ranging from 1.569 to 20.49%.

The PCSA of RF, VL, VM, BFL, and ST muscles in symptomatic sides of patients (15.85 cm^2, 28.18 cm^2, 21.53 cm^2, 11.67 cm^2 and 6.59 cm^2) were significantly lower than those in the healthy controls (19 cm^2, 36.32 cm^2, 23.37 cm^2, 14.15 cm^2 and 7.12 cm^2), respectively (Fig. 2). The PCSA of RF, VL, VM, and BFL on the asymptomatic side (16.75 cm^2, 30.4 cm^2, 21.4 cm^2 and 12.41 cm^2) were significantly lower than those in the healthy control group. The PCSA of VL and BFL on the symptomatic side were significantly lower than those on the asymptomatic side (30.4 cm^2 and 12.41 cm^2).

Regarding EI, the symptomatic side showed significantly higher values for RF, VL, VM, BFL, and ST muscles in patients (128.95, 121.12, 105.72, 90.52 and 93.15) than in the healthy control group (100.39, 93.97, 88.14, 77.69 and 78.73). The EI on the asymptomatic side (115.35,

Table 4 Reliability statistics and measurement errors

	EI				PCSA				G			
	ICC	SEM	SEM (%)	P	ICC	SEM	SEM (%)	P	ICC	SEM	SEM (%)	P
RF	0.987	1.824	1.569	0.995	0.977	2.896	12.311	0.355	0.982	0.306	3.361	0.396
VL	0.987	1.908	1.714	0.272	0.995	4.001	15.742	0.365	0.971	0.406	5.065	0.370
VM	0.979	2.346	2.383	0.561	0.999	1.072	3.174	0.373	0.98	0.215	3.348	0.857
BFL	0.985	1.904	2.146	0.211	0.996	4.251	20.49	0.427	0.971	0.437	5.917	0.218
ST	0.98	2.056	2.301	0.702	0.999	0.847	6.694	0.241	0.971	0.384	4.626	0.374

RF Rectus Femoris, VM Vastus Medialis, VL Vastus Lateralis, BFL Biceps Femoris long head, ST Semitendinosus, P p-value, ICC Intra-class Correlation Coefficient, SEM Standard Error of Measurement

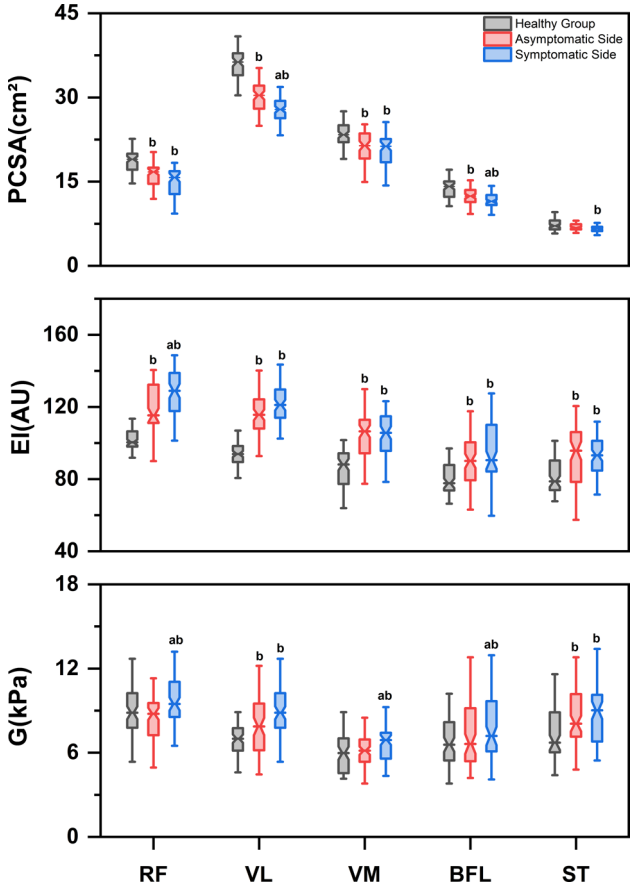

Fig. 2 Comparison of muscle features. Three datasets sequentially representing the healthy group (grey), asymptomatic side (red), and symptomatic side (blue). RF Rectus Femoris, VM Vastus Medialis, VL Vastus Lateralis, BF Biceps Femoris long head, ST Semitendinosus, PCSA physiological cross-sectional area, EI echo intensity, G shear modulus, AU arbitrary unit. **a** Compared to contralateral, $p < 0.05$. **b** Compared to the healthy group, $p < 0.05$

115.67, 106.5, 90.09, and 95.73) were also significantly elevated compared to the healthy controls. Significant differences in EI of RF were observed between the symptomatic and asymptomatic sides in patients.

For G, the symptomatic side values for RF, VL, VM, BFL, and ST in patients (9.48 kPa,7.88 kPa,6.9 kPa,7.2 k Pa and 9.03 kPa) were significantly higher than those in the healthy control group (8.85 kPa, 5.28 kPa, 5.98 kPa, 6.58 kPa and 6.73 kPa). The values for VL and ST on the asymptomatic side (7 kPa and 8.08 kPa) were also significantly higher compared to the healthy controls. The symptomatic side RF and VM values were significantly higher than those on the asymptomatic side (8.78 kPa and 6.15 kPa).

Subsequent analysis revealed an inverse correlation between the PCSA and the EI of RF, VL, VM and ST on the symptomatic side. In contrast, the G exhibited a positive correlation with EI for RF, VL, VM, BFL, and ST on the symptomatic side (Table 5).

Correlations between muscle characteristics and knee joint functional scores

The stepwise regression analysis (Table 6) indicated that the G of BFL and ST, as well as the EI of VM, had significant negative impacts on the HSS total score (Beta = -0.388, Beta = -0.323, Beta = -0.3). Conversely, the PCSA of BFL positively influenced the HSS total score (Beta = 0.492). The G of BFL exhibited a significant negative predictive effect on the KSS total score (Beta = -0.603), while its PCSA had a positive effect (Beta = 0.419). Increases in the G for VM, BFL, and ST, as well as the EI of VM, were associated with elevated WOMAC total scores (Beta = 0.2, Beta = 0.178, Beta = 0.792). An increase in the PCSA of BFL was associated with a decrease in the WOMAC total score (Beta = -0.181).

The PLS analysis revealed that the best predictors for the HSS score were the PCSA and G of BFL, the EI and G of ST, and the EI of RF (importance scores: 1.874, 1.408, 1.04, 1.01, and 1.073) (Fig. 3). For the KSS total score, the most influential features were the G and PCSA of BFL, the G and PCSA of RF, and the EI of BFL (importance values: 2.167, 1.699, 1.199, 1.078, and 1.069). In the case of the WOMAC score, the five key features were the EI of VM, the PCSA, and G of BFL, the G of VM and the EI of RF (importance values: 1.834, 1.555, 1.486, 1.062 and 1.061).

Table 5 Relationship between muscle echo intensity and other muscle parameters

		EI				
		RF	VL	VM	BFL	ST
PCSA	r	-0.787	-0.457	-0.933	0.207	-0.265
	(95% CI)	(-0.862~-0.679)	(-0.623~-0.252)	(-0.958~-0.895)	(-0.026 ~ 0.419)	(-0.468~-0.036)
	P	< 0.001	< 0.001	< 0.001	0.082	0.025
G	r	0.879	0.863	0.889	0.730	0.767
	(95% CI)	(0.813 ~ 0.923)	(0.789 ~ 0.912)	(0.828 ~ 0.929)	(0.600 ~ 0.823)	(0.651 ~ 0.848)
	P	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

Spearman correlation coefficients were calculated to analyze the correlation between muscle characteristics

RF Rectus Femoris, VM Vastus Medialis, VL Vastus Lateralis, BFL Biceps Femoris long head, ST Semitendinosus, PCSA physiological cross-sectional area, EI echo intensity, G shear modulus, CI Confidence intervals, P p-value

* $p < 0.05$, ** $p < 0.01$

Table 6 Stepwise regression analysis outcomes: assessing the impact of muscle characteristics on knee function scores

Scores	Muscle Characteristics	Standardized Coefficients (Beta)	Regression coefficients (95% CI)	*P*
HSS				
	BFL_G	-0.388	-0.733 (-1.070 ~ -0.396)	0.000
	ST_G	-0.323	-0.807 (-1.262 ~ -0.352)	0.001
	BFL_PCSA	0.492	1.581 (0.977 ~ 2.185)	0.000
	VM_EI	-0.300	-0.102 (-0.165 ~ -0.038)	0.003
KSS				
	BFL_G	-0.603	-2.005 (-2.562 ~ -1.447)	0.000
	BFL_PCSA	0.419	2.368 (1.420 ~ 3.315)	0.001
WOMAC				
	BFL_G	0.178	0.724 (0.190 ~ 1.258)	0.010
	ST_G	0.200	1.078 (0.357 ~ 1.800)	0.005
	BFL_PCSA	-0.181	-1.250 (-2.207 ~ -0.292)	0.013
	VM_EI	0.792	0.578 (0.477 ~ 0.678)	0.000

RF Rectus Femoris, VM Vastus Medialis, VL Vastus Lateralis, BFL Biceps Femoris long head, ST Semitendinosus, WOMAC Western Ontario and McMaster Universities Arthritis Index, KSS American Knee Society Score, HSS Hospital for Special Surgery

PCSA physiological cross-sectional area, EI echo intensity, G shear modulus, CI Confidence intervals, P p-value

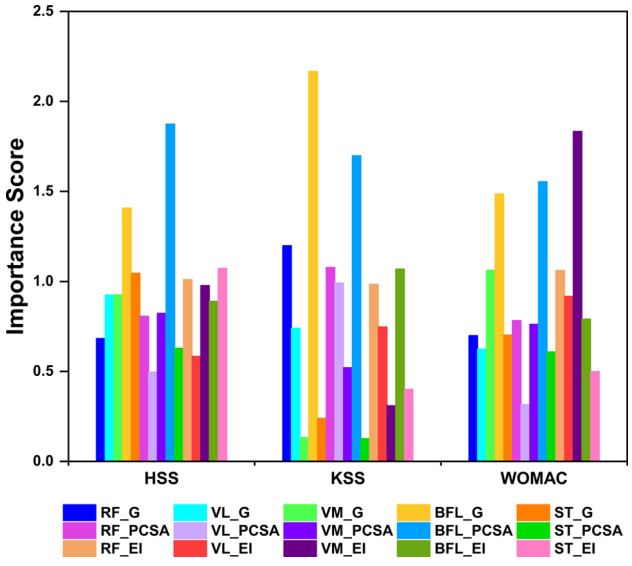

Fig. 3 Ranking of the importance of muscle characteristics for the impact on various knee function scores. RF Rectus Femoris, VM Vastus Medialis, VL Vastus Lateralis, BF Biceps Femoris long head, ST Semitendinosus, PCSA physiological cross-sectional area, EI echo intensity, G shear modulus, WOMAC Western Ontario and McMaster Universities Arthritis Index, KSS American Knee Society Score, HSS Hospital for Special Surgery

Discussion

US and SWE were used to quantitatively assess thigh muscle morphology, composition, and mechanical properties, including PCSA, EI, and G in female patients with severe KOA. The changes in thigh muscle characteristics and their interrelationships, as well as the association and impact of these characteristics on physical function, were analyzed. Compared to the healthy control group, the symptomatic side of KOA patients demonstrated significantly lower PCSA values, higher EI values, and elevated G values. The increases in intramuscular fat content in KOA patients that may impair the muscle morphology and alter the mechanical properties. The PCSA and G of the BFL emerge as the most significant muscle parameter influencing all knee function scores (HSS, KSS, WOMAC).

In this study, the PCSA of the VL and BFL on the symptomatic side of KOA patients was significantly lower by 22.4% and 17.5%, respectively, compared to the controls, suggesting a considerable degree of muscle loss. The evidence for atrophy of VL in KOA patients is compelling [8, 53, 54]. In elderly KOA patients with K-L grades II and III, the VL pennation angle and muscle thickness were significantly lower compared to those of healthy controls, in addition to decreases in isometric and concentric peak torque [10]. Although studies on hamstring morphological changes on the symptomatic side are limited [55], no significant differences in hamstring thickness between KOA patients and healthy controls have been identified. Arthrogenic muscle inhibition, contributing to muscle atrophy and weakness, is common in KOA patients [56]. Given the frequent quadriceps atrophy in KOA, it is plausible to infer similar hamstring atrophy in this population. The co-activation of BFL and VL during dynamic movements in KOA patients is well-documented [57], potentially explaining the concurrent atrophy. Thigh muscle weakness and adiposity are pivotal risk factors in KOA progression [8]. As VL and BFL are the strongest muscles in the quadriceps and hamstrings [58], the lower PCSA values in both muscles are associated with a significant difference in muscle force and knee function [50]. Early detection and monitoring of morphological changes in VL and BFL are crucial for effective disease management.

The PCSA of muscles on the asymptomatic side was reduced compared to the healthy control group, particularly in VL and BFL, which decreased by 19.47% and 14%. This atrophy may result from inter-limb effects

and compensatory mechanisms. Due to these inter-limb effects, the muscles on the asymptomatic side of KOA patients may atrophy as a result of pain, functional impairment, and disuse of homologous muscles on the symptomatic side [59]. Regarding compensatory mechanisms, the pain and functional restrictions on the symptomatic side may induce a heightened dependency on the asymptomatic side for weight-bearing tasks. This shift in load distribution can precipitate overuse and ultimately lead to muscle damage and atrophy on the asymptomatic side [60]. We also found that the PCSA of VL and BFL on the asymptomatic side was higher than on the symptomatic side. Tsukada et al. [54] found that the muscle volume of the symptomatic side in female KOA patients was approximately 6% smaller than that of the asymptomatic side, which aligns with our observations. The differences in PCSA between the symptomatic and asymptomatic sides in our study revealed muscular asymmetry in the lower limbs of KOA patients. The asymmetry in leg muscle mass in elderly KOA patients is associated with the prevalence of KOA, the severity of radiographic findings, and the prevalence of knee pain [61]. Early evaluation of VL and BFL parameters is pivotal for identifying muscular asymmetry and developing a targeted muscle intervention strategy that guides functional exercise protocols.

An inverse correlation was detected between PCSA and EI in RF, VL, VM, and ST on the symptomatic side, contrasted by a positive correlation between G and EI in RF, VL, VM, BFL, and ST. Our findings suggest that intramuscular fat content significantly affects muscle morphological structure and mechanical properties, primarily manifesting as alterations in pennation angle and material properties. Firstly, the magnitude of the pennation angle is crucial for the efficiency of force transmission between muscle fibers and tendons [62]. Substantial fatty infiltration into the spaces created by architectural changes may alter it [63]. In patients with KOA, a decrease in the pennation angle has been observed with the increased intramuscular fat infiltration [9]. A reduced pennation angle signifies a decrease in the number of parallel-aligned muscle fibers that contribute to force production [30], and the PCSA is a representative measure of these fiber numbers [62]. This may account for the observed negative correlation between EI and PCSA, as intramuscular fat infiltration likely leads to a decrease in PCSA by diminishing the pennation angle. Secondly, fat has stiffer material properties than muscle, muscles with a higher intramuscular fat content exhibit stiffer material properties, which may resist muscle fiber shortening and reduce muscle flexibility [30]. These findings elucidate the underlying mechanisms through which fat infiltration reduces muscle force generation and highlight the pivotal importance of addressing fat infiltration in the clinical treatment of KOA. Our results also revealed a significant difference in EI of the RF between the symptomatic and asymptomatic sides, which may be associated with the unique morphological structure of the RF. Among the quadriceps muscles, only the RF possesses a complicated tendon-aponeurosis complex, such as central aponeurosis (CA) [64]. It has been reported that in patients with KOA, morphological changes of the CA of the symptomatic-side RF are present, such as a shorter CA length and irregular CA curvature [64]. These muscular morphological changes are likely to result in the formation of new acoustic reflection planes within the RF of the symptomatic side, thereby contributing to an increase in EI [25].

Muscle stiffness on the symptomatic side of KOA patients was significantly elevated compared to the healthy control group, with the G values for the quadriceps increasing by 20.65% and for the hamstring by 10.75%. Modifications in muscle stiffness among KOA patients could be associated with pain, excessive muscle activity, and intramuscular fat infiltration. First, pain is recognized to markedly increase muscle stiffness in individuals, with a positive correlation between muscle stiffness and pain severity [52]. Second, KOA patients often stabilize their knee joints through excessive co-contractions, which elevate local metabolic demands and capillary pressure, increasing muscle stiffness [65]. Third, muscle stiffness may also result from intramuscular fat infiltration [66], leading to increased stiffness by reducing fiber stress and creating a more rigid structure that diminishes force generation [30].

We observed that elevated muscle stiffness and fat infiltration within the thigh muscles may intensify the impairment of knee joint function, while an augmentation in muscle mass has the potential to facilitate the amelioration of knee joint functionality. In particular, the PCSA and G of BFL were identified as the best predictors of all knee joint function scores. PCSA, indicative of muscle strength, and G, reflecting muscle stiffness, this finding highlights the vital role of the hamstring muscles in the knee joint function in patients with KOA. The functional status of both the quadriceps and hamstrings is crucial for healthy knee joint function, however, in patients with severe KOA, the decline in quadriceps function far exceeds that of the hamstrings. Compared to a healthy control group, KOA patients displayed a significant lower level of knee extension strength ranging from 25 to 45%, whereas knee flexion strength was found to be 19–25% less [67]. Moreover, KOA patients demonstrated higher hamstring-to-quadriceps moment ratios, indicating that the hamstrings undergo functional changes to compensate for the insufficient strength of the quadriceps [68]. These finding emphasizes the critical role of the hamstrings in maintaining knee joint function

and mechanical balance in KOA patients, particularly when quadriceps function is compromised. In contrast to healthy individuals, KOA patients exhibit increased hamstring muscle force during walking [69], as well as excessive co-contraction of the lateral hamstrings and quadriceps [70]. This strategy may serve to maintain dynamic stability of the knee joint, without any further increase in medial contact loading [71].Furthermore, the increased stiffness and decreased flexibility of the hamstring muscles in KOA patients adversely affect knee joint function [20], not only intensifying patellofemoral joint stress but also potentially leading to pain and physical function impairment [72]. These findings enhance the importance of enhancing hamstring strength and flexibility to improve the daily activity performance of KOA patient, a notion that resonates with previous research. Strengthening of the hamstrings in addition to strengthening of the quadriceps has been shown to be effective in reducing pain, expanding the range of motion, and enhancing functional performance among KOA patients [73]. Furthermore, targeting the flexibility of the hamstring muscles specifically can contribute to symptom relief and an improvement in WOMAC scores [74].

This study also identifies the EI of the VM as a significant predictor of the WOMAC score. The EI of the VM reflects the level of intramuscular fat infiltration, and as a vital component of the knee extensor group, the VM`s fat infiltration is closely associated with extensor weakness [22].Extensor weakness is a pivotal risk factor for the exacerbation of pain, functional impairment, and symptom deterioration in KOA patients [75], which may account for the widely observed correlation between the EI of VM and the impairment of knee joint function in individuals with knee osteoarthritis [76]. The WOMAC score, widely utilized for assessing the primary symptoms of KOA in daily living, serves as a critical tool for evaluating the severity and progression of the disease [77]. It is particularly valuable for tracking the dynamic changes of the disease through variations in score [78]. Consequently, the profound impact of the EI of VM on the WOMAC score underscores its clinical significance in monitoring the progression of KOA.

Our findings quantitatively characterized thigh muscle features in severe KOA, revealing a significant correlation between knee function scores and various muscle parameters, such as muscle morphological structure, intramuscular fat, and muscle stiffness. These findings may have implications for refining diagnostic criteria and tailoring personalized rehabilitation strategies in KOA management. Muscle morphological alterations, such as a marked reduction in PCSA values, compromise muscular strength and elevate the risk of falls, thereby exacerbating joint degeneration and accelerating disease progression [5, 79]. This underscores the importance of targeting muscle morphological structure in treatment to alleviate joint burden, mitigate KOA-related joint pain and dysfunction [80], and enhance patient mobility and quality of life [80]. Intramuscular fat infiltration exacerbates joint inflammation, hampers mobility, and heightens pain in KOA patients [26]. Our study revealed that the extent of muscle fat infiltration profoundly influences knee joint function, with the EI of VM emerging as a key determinant of WOMAC scores. To counteract this, modifying dietary habits and incorporating aerobic exercise can reduce intramuscular fat, bolster muscle strength, and alleviate clinical symptoms in KOA patients [81]. Abnormal muscle stiffness, as evidenced by a higher shear modulus, restricts joint mobility and accelerates joint degeneration [18], and is closely associated with pain and joint dysfunction in KOA patients [8]. As a solution, interventions such as physical therapy and massage, which aim to reduce muscle stiffness, can alleviate pain, improve joint flexibility, and play a significant role in the management and rehabilitation of KOA [67].

This study has certain limitations. We only included patients with severe KOA (KL grade III & IV), precluding insights into how muscle characteristics may change over the course of disease progression. Future longitudinal studies should investigate how muscle characteristics evolve across different KL grades and their relationship with clinical outcomes. Furthermore, the role of calf muscles, such as the gastrocnemius, was not examined in this study despite their importance in knee function, suggesting an area for future research.

Conclusions

Compared to healthy controls, the PCSAs in muscles on both sides of KOA patients were notably lower, with the VL muscle exhibiting a greater than 20% decrease on the symptomatic side, suggesting significant muscle atrophy and associated diminished strength. The G value, which represents the stiffness of the quadriceps and hamstring muscles on the symptomatic side, is up to 20.65% greater, suggesting poor flexibility of muscle fibers and elevated passive tension. EI for muscles on both sides of KOA patients was notably greater, with the VL muscle on the symptomatic side showing an addition of over 23.88%. A higher EI indicates a higher intramuscular fat content, which leads to a fewer number of contractile components within the muscle and consequently a lower muscle force. G, PCSA, and EI are all closely correlated with function scores. Especially, the G of BFL and ST, as well as the EI of VM, had a significant negative impact on knee joint function, whereas the PCSA of BFL had a significant positive effect. The results from this study may help understand the underlying mechanisms of muscle dysfunction in KOA patients and offer valuable insights for the development of more effective exercise therapies aimed at

preventing muscle degeneration and enhancing physical functionality. These findings highlight key muscle characteristics, such as G and PCSA, that could be used as reliable markers for early diagnosis and personalized rehabilitation strategies in KOA management.

Abbreviations

KOA	Knee osteoarthritis
BMI	Body mass index
KL	Kellgren-Lawrence
WOMAC	Western Ontario and McMaster Universities Arthritis Index
KSS	American Knee Society Score
HSS	Hospital for Special Surgery
CI	Confidence intervals
P	P-value, PCSA Physiological cross-sectional area
EI	Echo intensity
G	Shear modulus
RF	Rectus Femoris
VM	Vastus medialis
VL	Vastus lateralis
BF	Biceps femoris long head
ST	Semitendinosus
CSA	Cross-sectional area
US	Ultrasound
MRI	Magnetic resonance imaging
MT	Muscle thickness
PLS	Partial least squares

Supplementary Information

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Supplementary Material 1

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Not applicable.

Author contributions
T. L. is responsible for the study design, the collection and analysis of experimental data, the interpretation of results, and manuscript preparation. H. X. is responsible for data analysis and processing. S. Y. is responsible for data analysis and interpretation of results. J. Z. is responsible for study design, interpretation of results, and manuscript preparation. K. Z. is responsible for study design, data analysis, interpretation of results, and manuscript preparation. All authors reviewed the results and approved the final version of the manuscript.

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Data availability
The datasets used and analysed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
Ethical approval for this study was granted by Capital Medical University(2022SY122). During the conduct of this research, we adhered to the ethical guidelines set forth in the Declaration of Helsinki. Written informed consent was obtained from all participants.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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