



Research article

Degeneration of the cartilage quality is correlated with a higher intramuscular fat infiltration of the vastus medialis in older adults with pre-to-mild knee osteoarthritis

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ABSTRACT

Purpose: To quantitatively verify whether degeneration in the quality of the medial femoral cartilage is correlated with muscle volume loss and intramuscular adipose tissue (IntraMAT) infiltration in quadriceps using magnetic resonance imaging (MRI).

Methods: Of the 66 older adult participants ≥ 60 years old (74.5 ± 6.9 years), 29 were female. All participants were patients with pre-to-mild knee osteoarthritis. Muscle volume and IntraMAT infiltration of the four individual muscles, the rectus femoris (RF), vastus medialis (VM), vastus intermedius, and vastus lateralis were assessed, using proton density-weighted and 2-point Dixon MR images. Based on the MRI T2 mapping, the T2 relaxation times of the weight-bearing surface of the medial femoral cartilage were calculated. Simple linear regression analyses were performed, evaluating the correlations between the T2 relaxation time of the medial femoral cartilage and quadriceps muscle volume and IntraMAT. Multiple linear regression analysis using a stepwise method was performed, determining which indicators of the four individual muscles correlated with cartilage quality degeneration.

Results: Simple linear regression analyses revealed that a longer T2 relaxation time of the medial femoral cartilage was positively correlated with IntraMAT infiltration of the entire quadriceps muscle, RF, and VM, however not with the quadriceps muscle volume. Multiple linear regression analysis revealed that VM IntraMAT was particularly correlated with the extension of T2 relaxation time of the medial femoral cartilage.

Conclusions: In older adults with pre-to-mild knee osteoarthritis, IntraMAT infiltration of the quadriceps muscles, particularly of the VM was correlated with degeneration in the quality of the medial femoral cartilage.

1. Introduction

Quadricep muscle degeneration is common in patients with knee

osteoarthritis (OA) [1]. To evaluate muscle degeneration quantitatively and non-invasively, measuring muscle volume loss using magnetic resonance imaging (MRI) is essential [2]. In addition, recently,

Abbreviations: B, unstandardized regression coefficient; B, standardized regression coefficient; CI, confidence interval; CSA, cross-sectional area; IL-6, interleukin-6; IntraMAT, intramuscular adipose tissue; KL grade, Kellgren-Lawrence grade; MRI, magnetic resonance imaging; OA, osteoarthritis; ROI, regions of interest; RF, rectus femoris; SD, Standard deviations; TE, echo time; VM, vastus medialis; VL, vastus lateralis; VI, vastus intermedius; WORMS, whole-organ magnetic resonance imaging score.

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intramuscular adipose tissue (IntraMAT) infiltration also has been quantified, using chemical shift-based 2-point Dixon water-fat separation MRI techniques [3]. Both decreasing muscle volume and worsening IntraMAT infiltration are distinctive in patients with knee OA [4,5]. These characteristics of muscle degeneration are related to the progression of knee OA, presenting with the aggravation of knee symptoms, functional disability, and increased risk of artificial joint replacement [6–9]. In particular, recently, IntraMAT infiltration of the quadriceps muscles has garnered attention, because the changes thereof precede muscle volume loss in the early stages of knee OA [10].

Degeneration of the quadriceps muscles, caused by IntraMAT infiltration is associated with structural joint abnormalities in patients with knee OA. Previous studies have revealed that severe IntraMAT infiltration of the quadriceps muscles, particularly of the vastus medialis (VM) is related to the future progression of cartilage degeneration, such as the loss of thickness and worsening of the morphological score (whole-organ magnetic resonance imaging score: WOMIS) [11–13]. However, all the aforementioned studies have included patients with terminal-stage knee OA who have presented with severe cartilage damage and IntraMAT infiltration of the quadriceps muscles; only focusing on the association with cartilage volume loss. Cartilage compositional changes, such as proteoglycan loss or increased water content of the cartilage tissue occur in the early stages of knee OA, particularly without remarkable cartilage thinning [14–16]. However, no studies have investigated whether degeneration of cartilage quality, caused by compositional changes in early knee OA is associated with quadriceps muscle degeneration.

MRI T2 mapping is one of the gold standards for assessing cartilage quality [17]. This is an assessment of the increasing water content of the cartilage and can quantitatively detect the degeneration of cartilage quality, which is difficult to observe with the naked eye, as an extension of T2 relaxation times [18]. To the best of our knowledge, no study has investigated whether T2 relaxation times of the cartilage are correlated with quadriceps muscle volume and quality. Moreover, whether differences exist in the association with the degeneration of the cartilage quality among the four individual quadriceps muscles has not been elucidated. Thus, theoretically, necessity for further research lies in the early assessment of quadriceps muscle degeneration, to prevent the progression of knee OA and provide important findings for clinical settings.

Consequently, the purpose of this study was to quantitatively verify whether degeneration in the quality of the medial femoral cartilage is correlated with quadriceps muscle degeneration, using MRI, in older adults with pre-to-mild knee OA. We hypothesized that IntraMAT infiltration of the quadriceps muscles, particularly of the VM is correlated with the degeneration in the quality of the medial femoral cartilage.

2. Material and methods

2.1. Participants

In total, 66 community-dwelling older adults aged >60 years old participated in this study. The inclusion criteria were as follows: 1) no diagnosis of severe knee OA (Kellgren-Lawrence [KL] grade ≥ 3 [14,19]), and 2) could walk without any assistive devices. The exclusion criteria were as follows: 1) past surgical history involving the lower limb, 2) rheumatoid arthritis or a neuromuscular ailment, and 3) contraindications for MRI.

All participants were informed of the study aims and project briefings, and written informed consent was obtained before the study was initiated. This study was approved by **. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

2.2. MRI imaging

MR images of the thigh and knee joints of the right lower limb were acquired in the supine and knee extension position, using 3.0 Tesla scanners (MAGNETOM Verio; Siemens AG, Erlangen, Germany) and body coils. Before scanning, the participants rested on the bed for > 15 min to eliminate the effects of any condition of daily living (e.g. the T2 relaxation time of knee cartilage is immediately decreased after loading [20]). For the whole knee joints, three-dimensional-Sampling Perfection with Application optimized Contrast using different flip angle Evolutions (3D SPACE) with proton density-weighted and multi-echo images were acquired. Additionally, multi-slice, spin-lattice relaxation time (T1)-weighted and two-point Dixon images of the thigh muscles were acquired. The detailed parameters of all MR images are presented in Table 1. The entire scan took 18 min and 25 s. Using the two-point Dixon sequence, images of the water and fat ratios were obtained by computing the difference in signal intensities, based on the chemical shift between the in-phase and opposed-phase (Fig. 1). The IntraMAT was calculated using the following equation:

$$\text{IntraMAT}(\%) = \frac{\text{meansignalintensityoffat} \times 100 / (\text{meansignalintensityoffat} + \text{meansignalintensityofwater})}{100} \quad (1)$$

2.3. Evaluation of knee OA severity

The severity of OA of the tibiofemoral joint was assessed by an orthopedic surgeon using 3D SPACE with proton density-weighted images of the knee [10]. The assessment focused on several indicators of OA, including the degeneration of the cartilage and meniscus, presence of osteophytes, bone marrow edema, and subchondral cysts. Knee OA severity was graded on a scale of 0 (no OA) to 4 (severe OA). As per the findings of a previous study, this grading system has been confirmed to have excellent inter- and intra-observer agreements and is highly consistent with radiographic knee OA assessment using the KL grade, which classifies OA in five grades with radiological signs [21].

2.4. Quantification of the quadriceps muscle volume and intramuscular fat

Using OsiriX MD (version 11.0; OsiriX, Geneva, Switzerland), the regions of interest (ROI) of the rectus femoris (RF), VM, vastus intermedius (VI), and vastus lateralis (VL) were manually segmented on the

Table 1
Parameters of the magnetic resonance imaging for each sequence.

	proton density weighted image	multi-echo image	T1 weighted image	2-point dixon image
target domain	knee	knee	thigh	thigh
repetition time	1000 ms	2200 ms	2820 ms	4.33 ms
echo time	35 ms	10.4, 20.8, 31.2, 41.6, 52.0, 62.4, 72.8, 83.2 ms	16 ms	1.31, 2.54 ms
flip angle	120°	180°	129°	9°
slice thickness	0.7 mm	2.5 mm	4 mm	3 mm
interslice gap	—	2.5 mm	—	—
field of view	150 × 150 mm	160 × 300 mm	320 × 240 mm	286.4 × 365 mm
voxel size	0.59 × 0.59 × 0.7 mm ³	0.5 × 0.5 × 2.5 mm ³	0.5 × 0.5 × 4.0 mm ³	0.5 × 0.5 × 3.0 mm ³

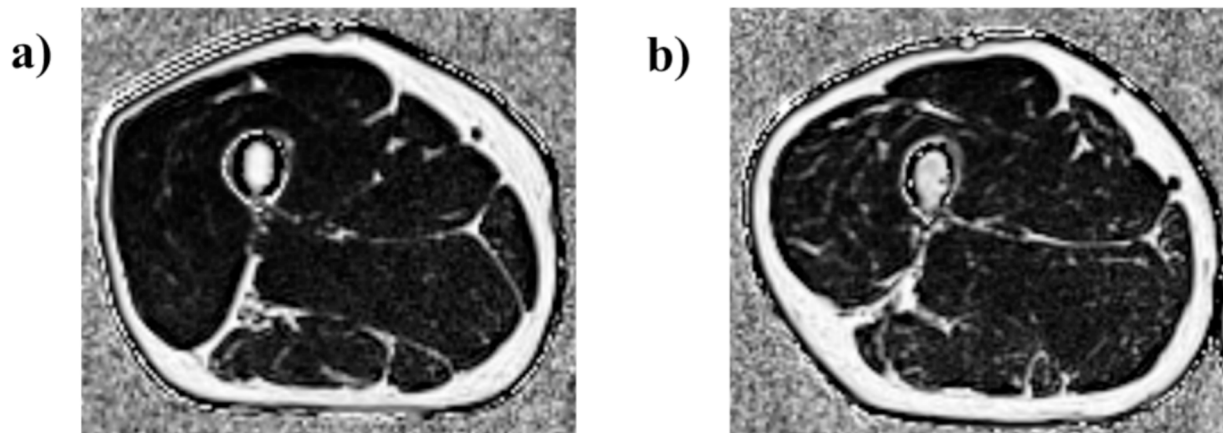


Fig. 1. Representative MR images of quadriceps muscles with low IntraMAT (%) and high IntraMAT (%). Image (a) is indicated as quadriceps muscles with low IntraMAT (%), and image (b) is indicated as quadriceps muscles with high IntraMAT (%). The knee OA severity of participants (a) and (b) were both grade 1. The voxels with high signal intensity of MR images are equivalent to the intramuscular adipose tissue.

MR images. Muscle volume was calculated using multi-slice T1-weighted images. Subsequent to the ROI segmentation of all slices of the MR images, the muscle cross-sectional area (CSA, cm^2) of each slice was measured. The CSA of each muscle multiplied by a slice thickness of 4 mm was summed as the muscle volume (cm^3). The volume of the entire quadriceps muscle was defined as the total value of the volumes of the four individual muscles. IntraMAT was calculated using two-point Dixon imaging. First, we segmented the ROI of the RF, VM, VI, and VL on the slice at the midpoint, between the anterior superior iliac spine and proximal end of the patella. Thereafter, the aforementioned ROIs for

each muscle were traced on five consecutive proximal and distal slices, with a total of 10 slices. Finally, we adjusted each ROI to include only the individual target muscles, and the mean values of IntraMAT of each muscle were calculated (Fig. 2). Furthermore, the IntraMAT of the entire quadriceps muscle was calculated as follows:

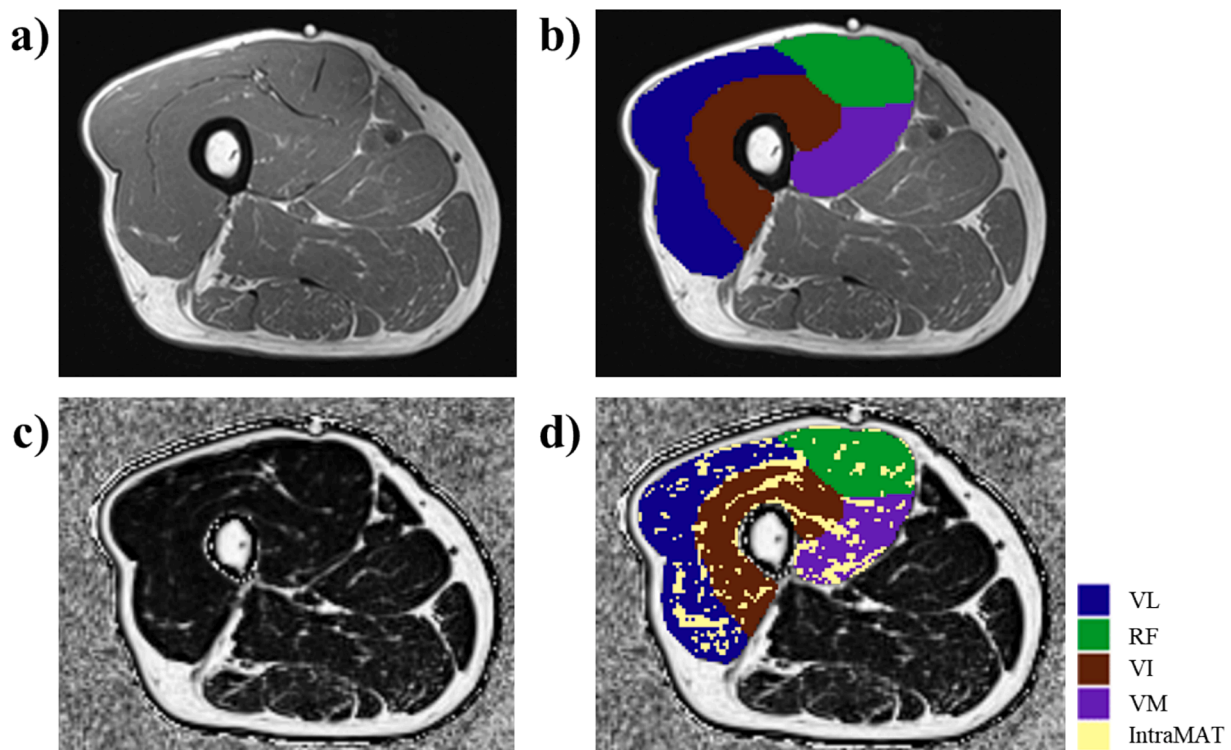


Fig. 2. The MR images to quantify the quadriceps muscle volume and intramuscular fat. a) To calculate the volume of each muscle (VL, RF, VI, and VM), T1 weighted images were used. b) The region of interests (ROIs) segmentation of all slices of the MR images were conducted. After the muscle cross-sectional area (CSA, cm^2) of each slice was measured, The CSA of each muscle multiplied by a slice thickness of 4 mm was summed as the muscle volume (cm^3). c) To calculate the IntraMAT of each muscle (VL, RF, VI, and VM), 2-point Dixon images were used. d) The ROIs were segmented on the slice at the midpoint, between the anterior superior iliac spine and the proximal end of the patella. These ROIs for each muscle were traced on five consecutive proximal and distal slices, with a total of 10 slices, and the mean values of IntraMAT of each muscle were calculated. VL: Vastus lateralis, RF: Rectus femoris, VI: Vastus intermedius, VM: Vastus medialis, IntraMAT: intramuscular adipose tissue.

$$\begin{aligned}
\text{QuadricepsIntraMAT}(\%) &= \text{RFIntraMAT}(\%) \\
&\times \frac{\text{RFVolume}(\text{cm}^3)}{\text{QuadricepsVolume}(\text{cm}^3)} + \text{VMIntraMAT}(\%) \\
&\times \frac{\text{VMVolume}(\text{cm}^3)}{\text{QuadricepsVolume}(\text{cm}^3)} + \text{VIIntraMAT}(\%) \\
&\times \frac{\text{VIVolume}(\text{cm}^3)}{\text{QuadricepsVolume}(\text{cm}^3)} + \text{VLIntraMAT}(\%) \\
&\times \frac{\text{VLVolume}(\text{cm}^3)}{\text{QuadricepsVolume}(\text{cm}^3)}
\end{aligned} \quad (2)$$

We confirmed the validity of the imaging analysis of each quadriceps muscle using the data of eight participants randomly selected in this study. The results indicated that the intraclass correlation coefficient (ICC [1,1]) of muscle volume (cm^3) was 0.890–0.995, and that of IntraMAT (%) was 0.788–0.988.

2.5. Evaluation of the T2 relaxation time of cartilage

Using the T2 mapping modules in 3D Slicer (<http://www.slicer.org/>), the T2 mapping images were produced from the multi-echo images of the knee. Subsequent to the logarithmic transformation of the signal intensity for each voxel, all values were fitted to the regression line in which the vertical and horizontal axes indicated the signal intensity and echo time (TE), respectively, based on the linear least-squares method. The reciprocal values of the slope of the regression line were subsequently calculated as the T2 relaxation times. Detailed information on the calculations is provided at: <https://github.com/gattia/Slicer-T2mapping>.

To improve the accuracy of the T2 mapping, the TE 10.4 s image was excluded from the calculation of the T2 relaxation time. Previous studies have demonstrated that a high accuracy of T2 mapping is achieved, by excluding the signal intensity of the image obtained from the shortest TE, during the MR sequence [22,23]. In addition, voxels with T2 relaxation times > 100 ms, or coefficients of determination (R^2) of regression lines, estimating T2 relaxation times < 0.7 were eliminated as outliers, caused by artifacts [24].

Subsequent to T2 mapping, T2 relaxation times of the weight-bearing surface of the medial and lateral femoral cartilage were measured using

3D slicer (<http://www.slicer.org/>). The weight-bearing surface of the femoral was defined as the area between the anterior margin of the anterior horn of the meniscus and posterior capsular attachment of the posterior horn of the meniscus, based on the segmentation of WORMS [25]. On the TE 10.4 ms image, a slice that was clearly visible in the anterior and posterior horns of the meniscus was detected; and the ROIs were manually segmented. The ROIs were subsequently reflected on the T2 mapping image, and the means of the T2 relaxation times of all ROIs were calculated (Fig. 3).

We confirmed the validity of the imaging analysis of cartilage using the data of eight participants randomly selected in this study. The results indicated that the intraclass correlation coefficient (ICC [1,1]) of T2 relaxation times (ms) was 0.925.

2.6. Statistical analyses

All statistical analyses were conducted using IBM SPSS Statistics 22 (IBM SPSS, Armonk, NY, USA), and the threshold for statistical significance was set at $p < 0.05$. Simple linear regression analyses with and without adjustment for age, sex, height, and body mass were performed, to evaluate the correlations between the T2 relaxation times of the medial femoral cartilage and quadriceps muscle volume and IntraMAT. Furthermore, a multiple linear regression analysis with the T2 relaxation time of the medial femoral cartilage as a dependent variable; in addition to the muscle volume and IntraMAT of the four individual muscles as independent variables was performed. This was done to investigate which indicators of the four individual muscles were particularly correlated with the degeneration in the quality of the medial femoral cartilage. All indicators of the four individual quadriceps muscle volumes and IntraMAT were entered using a stepwise method; and the analysis was adjusted for age, sex, height, and body mass. In addition, as supplementary analyses to confirm whether the correlation with quadriceps muscle degeneration was specifically observed in the medial femoral cartilage, simple and multiple linear regression analyses with the T2 relaxation times of the lateral femoral cartilage as a dependent variable were performed. All independent and adjustment variables were entered using a method similar to that in the analysis of the medial femoral cartilage.

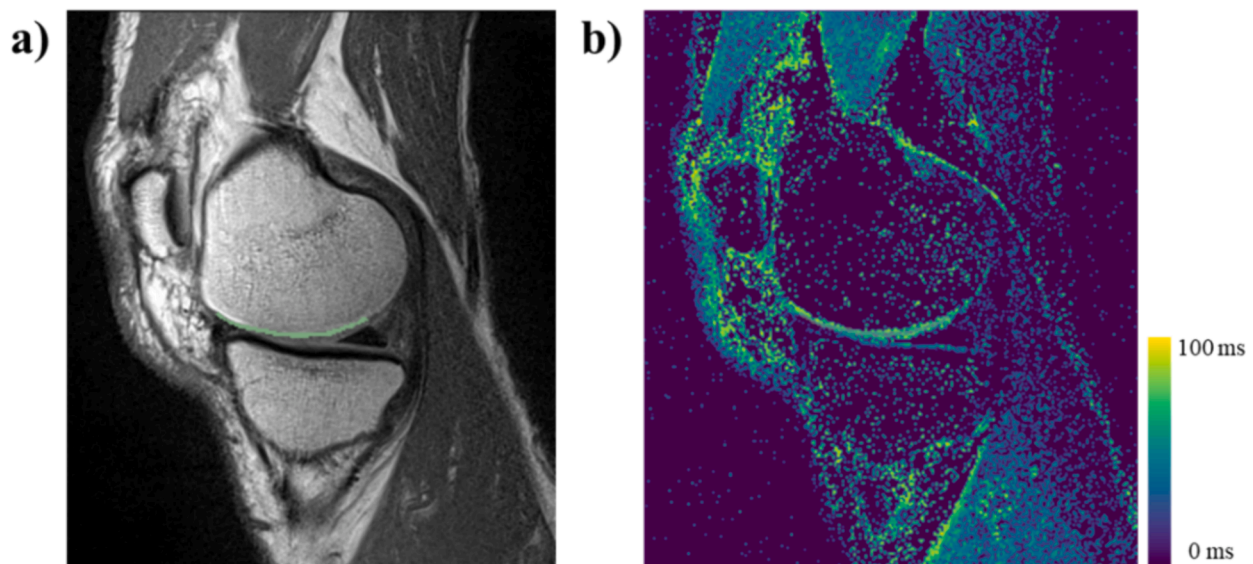


Fig. 3. The MR images to entire the T2 relaxation time of cartilage. a) The weight-bearing surface of the medial femoral was defined as the area between the anterior margin of the anterior horn of the meniscus and the posterior capsular attachment of the posterior horn of the meniscus [25]. The segmentation of region of interest (ROI) was performed manually on all slices of the medial femur. b) All ROIs were reflected on the T2 mapping image, and the means of the T2 relaxation times of all ROIs were calculated.

3. Results

The demographic and clinical characteristics of the 66 participants, means of the four individual quadriceps muscle volumes, and IntraMAT are depicted in Table 2. No participants were graded as severe knee OA in this study as a result of the assessment using MRI [21]. Knee OA severity was distributed as grade 0, $n = 20$ (women, 25.0 %); grade 1, $n = 31$ (women, 61.3 %); and grade 2, $n = 15$ (women, 33.3 %).

The results of the simple linear regression analyses revealing the correlations of the T2 relaxation times of the medial femoral cartilage and quadriceps muscle volume and IntraMAT are shown in Table 3. The volume of the quadriceps muscles was negatively correlated with the T2 relaxation times of the medial femoral cartilage, and lower volumes of the entire quadriceps and each individual muscle were correlated with a longer T2 relaxation time of the medial femoral cartilage (all $p < 0.001$). However, these correlations were not observed after adjusting for age, sex, height, and body mass. Conversely, the IntraMAT of the quadriceps muscles was positively correlated with the T2 relaxation times of the medial femoral cartilage, and worse IntraMAT infiltration of the VM was correlated with a longer T2 relaxation time of the medial femoral cartilage ($p = 0.005$). After adjusting for age, sex, height, and body mass, worse IntraMAT infiltration of the entire quadriceps muscle, RF, and VM was correlated with a longer T2 relaxation time of the medial femoral cartilage (entire quadriceps muscle, $p = 0.034$; RF, $p = 0.014$; VM, $p = 0.011$).

Multiple linear regression analysis using a stepwise method revealed that VM IntraMAT was the only independent variable correlated with the extension of the T2 relaxation time of the medial femoral cartilage (Table 4, unstandardized regression coefficient [B] = 0.876; 95 % confidence interval = 0.209 to 1.543; $p = 0.011$).

The results of supplemental analyses revealing the correlations of the T2 relaxation times of the lateral femoral cartilage and quadriceps muscle volume and IntraMAT are shown in Table 5. The volume of the quadriceps muscles was negatively correlated with the T2 relaxation times of the lateral femoral cartilage, and lower volumes of the entire quadriceps muscle were correlated with a longer T2 relaxation time of the lateral femoral cartilage (entire quadriceps muscle, $p = 0.001$; RF, $p = 0.011$; VM, $p = 0.002$; VL, $p = 0.002$; VI, $p = 0.001$). In addition, the IntraMAT of the VM was positively correlated with the T2 relaxation times of the lateral femoral cartilage, and worse IntraMAT infiltration of the VM was correlated with a longer T2 relaxation time of the lateral femoral cartilage ($p = 0.019$). However, in contrast to the medial femoral cartilage, these correlations were not observed after adjusting for age, sex, height, and body mass. Multiple linear regression analysis using a stepwise method also revealed that no independent variables correlated with the T2 relaxation time of the lateral femoral cartilage.

Table 2
Demographic and clinical characteristics of the participants.

	Mean $\pm$ SD or n (%)
Age, years	74.5 $\pm$ 6.9
Female sex	29 (43.9 %)
Height, cm	160.1 $\pm$ 8.9
Body mass, kg	54.6 $\pm$ 9.7
T2 relaxation time of femoral cartilage, ms	44.4 $\pm$ 5.6
Muscle volume, cm ³	
Quadriceps femoris	1144.4 $\pm$ 297.6
Rectus femoris	159.2 $\pm$ 41.8
Vastus medial	287.6 $\pm$ 79.7
Vastus lateralis	369.4 $\pm$ 98.7
Vastus intermedius	328.2 $\pm$ 91.5
IntraMAT, %	
Quadriceps femoris	7.7 $\pm$ 1.7
Rectus femoris	5.9 $\pm$ 1.5
Vastus medialis	7.9 $\pm$ 2.2
Vastus lateralis	8.2 $\pm$ 2.1
Vastus intermedius	7.7 $\pm$ 1.8

Intra-MAT: intramuscular adipose tissue, SD: Standard deviations.

4. Discussion

This is the first study to quantitatively verify whether degeneration in the quality of the medial femoral cartilage is correlated with quadriceps muscle degeneration, using MRI in older adults with pre-to-mild knee OA. Our results revealed that IntraMAT infiltration of the quadriceps muscles was correlated with the degeneration in the quality of the medial femoral cartilage, whereas no correlation was observed with muscle volume. Another important finding revealed that, among the quadriceps muscles, VM IntraMAT was particularly correlated with the degeneration in the quality of the medial femoral cartilage. Considering that this correlation was not observed in the lateral femoral cartilage, the VM IntraMAT infiltration may be specifically correlated with degeneration in the quality of the medial femoral cartilage in patients with pre-to-mild knee OA.

Simple linear regression analysis revealed a correlation between the cartilage degeneration and IntraMAT infiltration of the quadriceps muscles. Severe IntraMAT infiltration of the quadriceps muscles is known to affect the cartilage volume loss and worsens WORMS in patients with knee OA [11,13]. The extension of T2 relaxation times can detect an increase in the water content of the cartilage [18], which is a representative change in the cartilage composition, before thinning [14–16]. Thus, the findings of our study revealed that IntraMAT infiltration of the quadriceps muscles is additionally related to the degeneration of the cartilage quality, which is observable in the early-to-advanced stages of knee OA. The adipose tissue involved in the decline of muscle quality is known to emit inflammatory cytokines [26,27]; and an increase in interleukin (IL)-6, which is an inflammatory cytokine affects the degeneration of cartilage [5,28,29]. In animal experiments, post-intra-articular injection of IL-6, a reduction in the proteoglycan concentrations of the cartilage tissue was detected, suggesting an association between the changes in cartilage composition and inflammatory biomolecules [29,30]. The physiological mechanism by which IntraMAT infiltration contributes to cartilage degeneration remains unclear; however, a mutual relation with inflammation in OA may exist.

Simple linear regression analyses adjusted for age, sex, height, and body mass revealed the absence of a correlation between the degeneration of the cartilage quality and quadriceps muscle atrophy. This result is inconsistent with the findings of a previous study by Kumar et al. in 2014 which revealed a negative correlation between the cartilage degeneration and CSA of the quadriceps muscles [6]. However, this inconsistency can be deliberated. First, Kumar et al. [6] included patients with an advanced-to-terminal OA with a KL grade 3–4, whereas our study only targeted healthy older adults and patients with early to-mild knee OA. Second, their study [6] assessed cartilage degeneration, using the semi-quantitative morphological score, WORMS. Conversely, we assessed the degeneration in cartilage quality, using T2 relaxation times, which reflected the change in the amount of the water content of the cartilage. Both atrophy and IntraMAT infiltration of the quadriceps muscles have been observed in patients with knee OA [4,5]; nonetheless, only an increasing IntraMAT of the quadriceps muscles without a notable volume loss is a characteristic of the early stage of knee OA [10]. This could be a factor that has no significant association between degeneration of cartilage quality and quadriceps muscle atrophy.

Multiple linear regression analysis revealed that, among the quadriceps muscles, the VM IntraMAT was particularly correlated with degeneration of cartilage quality. In patients with knee OA, ectopic adipogenesis occurs in the VM [31]; and this degeneration is associated with the future progression of knee joint lesions [11]. In general, the VM is an important muscle that contributes to knee joint stability [11,32,33], playing an integral role in the efficient movement of knee joints. A recent anatomical study found that an additional medial-acting force produced by the VM contributes to the contraction of the entire quadriceps muscle, via the myofascial connections. This plays an important role in the effective generation of the quadriceps muscle

Table 3

Simple linear regression analysis revealing the correlations of the T2 relaxation time of the medial femoral cartilage and quadriceps muscle volume and IntraMAT.

	Crude value				Adjusted value			
	B	β	95 % CI	p value	B	β	95 % CI	p value
Muscle volume, cm ³								
Quadriceps femoris	−0.010	−0.534	−0.014 to −0.006	<0.001	−0.007	−0.379	−0.016 to 0.002	0.127
Rectus femoris	−0.068	−0.504	−0.097 to −0.039	<0.001	−0.033	−0.244	−0.082 to 0.016	0.188
Vastus medialis	−0.036	−0.513	−0.051 to −0.021	<0.001	−0.020	−0.286	−0.053 to 0.012	0.220
Vastus lateralis	−0.029	−0.509	−0.041 to −0.017	<0.001	−0.016	−0.271	−0.039 to 0.008	0.183
Vastus intermedius	−0.031	−0.510	−0.045 to −0.018	<0.001	−0.017	−0.272	−0.045 to 0.012	0.244
IntraMAT, %								
Quadriceps femoris	0.584	0.180	−0.215 to 1.384	0.149	0.871	0.268	0.068 to 1.673	0.034
Rectus femoris	0.752	0.199	−0.170 to 1.675	0.108	1.154	0.306	0.238 to 2.071	0.014
Vastus medialis	0.904	0.345	0.289 to 1.518	0.005	0.876	0.334	0.209 to 1.543	0.011
Vastus lateralis	0.074	0.027	−0.613 to 0.761	0.830	0.463	0.168	−0.216 to 1.142	0.178
Vastus intermedius	0.365	0.119	−0.397 to 1.128	0.342	0.646	0.210	−0.107 to 1.399	0.091

A single linear regression analysis has been conducted with age, sex, height, and body mass, as the adjustment variables. The results with and without adjustments are presented as crude and adjusted values, respectively. IntraMAT: intramuscular adipose tissue, B: unstandardized regression coefficient, β : standardized regression coefficient, CI: confidence interval.

Table 4

Multiple linear regression analysis revealing the correlations of the T2 relaxation time of the medial femoral cartilage and quadriceps muscle volume and IntraMAT.

	B	β	95 % CI	p value
Vastus medialis IntraMAT, %	0.876	0.334	0.209 to 1.543	0.011
Age, years	0.056	0.068	−0.127 to 0.239	0.546
Sex	−0.578	−0.051	−5.166 to 4.010	0.802
Height, cm	0.072	0.113	−0.155 to 0.298	0.529
Body mass, kg	−0.339	−0.585	−0.532 to −0.145	0.001

A multiple linear regression analysis has been conducted using a stepwise method, including the age, sex, height, and body mass, as adjustment variables. IntraMAT: intramuscular adipose tissue, B: unstandardized regression coefficient, β : standardized regression coefficient, CI: confidence interval.

force, during the entire range of motion [34]. Considering these findings, it can be inferred that VM dysfunction is possible to restrict efficient muscle exertion for knee extension. Moreover, increasing co-contraction of the VM and other knee muscles (e.g. semimembranosus muscle, biceps femoris, and VL) during the stance phase of gait is associated with a greater progression of future cartilage loss in patients with knee OA [35]. Incidentally, muscle co-contraction is one of the compensatory strategies for joint instability caused by muscle weakness [36]. Increased VM IntraMAT inflammation, which is a distinctive change in patients with early knee OA [10] can result in these dysfunctions of knee joint. This could partially explain the correlation found in our study between IntraMAT infiltration of the VM and the

degeneration of cartilage quality.

Clinically, maintaining or improving VM IntraMAT, rather than focusing solely on muscular hypertrophy, may contribute to the prevention of cartilage degeneration. Our finding emphasized the importance of VM IntraMAT for cartilage degeneration in not only the advanced to severe stage of knee OA but also the early stage of knee OA. Recently, in the clinical setting, the compositional degeneration of skeletal muscles, including an increased IntraMAT or non-contractile tissue has been conveniently evaluated, using ultrasound echo intensity or bioelectrical impedance analysis [37,38], which can be improved by muscle strength exercises [39–41]. Therefore, our findings can potentially contribute to the establishment of a strategy for preventing the progression of cartilage degeneration in knee OA.

This study had several limitations. First, only the cartilage degeneration of the weight-bearing surface of the femoral cartilage was evaluated. However, in the early stages of knee OA, because the femoral cartilage is more markedly degenerated than the tibial cartilage [42,43], the evaluations approximately encompassed the degeneration of the cartilage quality of the tibiofemoral joint. The correlation between cartilage degeneration in other compartments, such as the patellofemoral joint, and quadriceps muscle degeneration should be investigated. Second, the IntraMAT of the quadriceps muscles was partially evaluated with only 10 slices. However, previous studies have suggested that the distribution of the IntraMAT among the quadriceps muscles is constant [44,45]. Third, the sample size of our study was relatively small. The post-hoc power analysis for the multiple linear regression analysis, based on the adjusted coefficient of determination $R^2 = 0.294$, yielded a

Table 5

Simple linear regression analysis revealing the correlations of the T2 relaxation time of the lateral femoral cartilage and quadriceps muscle volume and IntraMAT.

	Crude value				Adjusted value			
	B	β	95 % CI	p value	B	β	95 % CI	p value
Muscle volume, cm ³								
Quadriceps femoris	−0.008	−0.397	−0.013 to −0.003	0.001	−0.004	−0.192	−0.015 to 0.007	0.457
Rectus femoris	−0.046	−0.311	−0.081 to −0.011	0.011	−0.005	−0.031	−0.062 to 0.052	0.871
Vastus medialis	−0.029	−0.373	−0.047 to −0.011	0.002	−0.007	−0.093	−0.045 to 0.030	0.702
Vastus lateralis	−0.024	−0.381	−0.039 to −0.009	0.002	−0.010	−0.157	−0.036 to 0.017	0.457
Vastus intermedius	−0.028	−0.412	−0.043 to −0.013	0.001	−0.015	−0.223	−0.048 to 0.017	0.356
IntraMAT, %								
Quadriceps femoris	0.541	0.151	−0.344 to 1.425	0.226	0.224	0.063	−0.772 to 1.171	0.637
Rectus femoris	0.999	0.241	−0.007 to 2.006	0.051	0.805	0.194	−0.272 to 1.881	0.140
Vastus medialis	0.831	0.288	0.141 to 1.521	0.019	0.254	0.088	−0.545 to 1.053	0.527
Vastus lateralis	−0.018	−0.006	−0.774 to 0.738	0.962	−0.013	−0.004	−0.798 to 0.771	0.973
Vastus intermedius	0.415	0.123	−0.424 to 1.254	0.327	0.185	0.055	−0.691 to 1.061	0.674

A single linear regression analysis has been conducted with age, sex, height, and body mass, as the adjustment variables. The results with and without adjustments are presented as crude and adjusted values, respectively. IntraMAT: intramuscular adipose tissue, B: unstandardized regression coefficient, β : standardized regression coefficient, CI: confidence interval.

power of 0.985, which confirmed that the statistical power was sufficient. However, our findings should be validated in a larger cohort study to assess their relevance to broader populations. Finally, this was a cross-sectional study; thus, the causal correlation between the cartilage degeneration and IntraMAT infiltration of the quadriceps muscles is unclear. Future longitudinal research is needed to identify this causal correlation.

5. Conclusion

In conclusion, in older adults with pre-to-mild knee OA, IntraMAT infiltration of the quadriceps muscles, particularly of the VM was correlated with futher, whereas no correlation was observed with muscle volume.

Author contributions

All authors have made substantial contributions to: 1) the conception and design of the study, 2) critical revision of important intellectual content, and 3) final approval of the version to be submitted. Specific contributions of the authors are as follows: 1) analysis and interpretation of the data and 2) drafting of the article: SO, MT, MaY, and NI.

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CRediT authorship contribution statement

Shogo Okada: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Masashi Taniguchi:** Writing – review & editing, Resources, Data curation, Conceptualization. **Masahide Yagi:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Yoshihiro Fukumoto:** Writing – review & editing, Methodology, Data curation, Conceptualization. **Tetsuya Hirono:** Writing – review & editing, Methodology, Data curation, Conceptualization. **Momoko Yamagata:** Writing – review & editing, Methodology, Data curation, Conceptualization. **Ryusuke Nakai:** Writing – review & editing, Methodology, Data curation, Conceptualization. **Masashi Kobayashi:** Writing – review & editing, Resources, Data curation, Conceptualization. **Noriaki Ichihashi:** Writing – original draft, Writing – review & editing, Supervision, Validation, Data curation, Formal analysis, Visualization, Methodology, Project administration, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Corrigendum



Corrigendum to “Degeneration of the cartilage quality is correlated with a higher intramuscular fat infiltration of the vastus medialis in older adults with pre-to-mild knee osteoarthritis” [Eur. J. Radiol. 183 (2025) 111930]

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The authors regret the following errors in the published article:

1. In page 2, the material and methods section, the original text stated, “This study was approved by **.”, but the correct description should

- be “This study was approved by the Ethics Committee of the Kyoto University Graduate School and Faculty of Medicine (R1746).”
2. In **Table 2**, “Vastus medial” should read “Vastus medialis.”

The authors would like to apologise for any inconvenience caused.

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Association of Muscle Quantity and Quality With Knee Extension Strength in Knee Osteoarthritis: The Nagahama Study

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Objective. We aimed to examine whether lower-limb muscle quantity and quality assessed by bioelectric impedance analysis (BIA) were associated with knee extension strength and whether the association differed with knee osteoarthritis (OA) severity.

Methods. We included 1,525 participants (63.6% women; mean $\pm$ SD age 68.0 $\pm$ 5.3 years) from the Nagahama Prospective Cohort. Knee extension strength was measured during maximum voluntary isometric contraction. Lower-limb muscle mass and the extracellular water (ECW)-to-intracellular water (ICW) ratio were used as indicators of muscle quantity and quality, respectively, and assessed via a BIA device. We executed multiple linear regression analyses to investigate the association of muscle quantity and quality with knee extension strength. Additionally, participants were classified into three groups with respect to OA severity and symptoms: control, early OA, and advanced OA groups; subgroup analyses were also executed.

Results. The muscle mass ($P < 0.001$) and ECW-to-ICW ratio ($P = 0.009$) were significantly associated with knee extension strength. In the subgroup analysis, the muscle mass was significantly associated with knee extension strength ($P < 0.001$), but there was no association between ECW-to-ICW ratio and knee extension strength ($P = 0.731$) in the control group. In the early OA and advanced OA groups, the muscle mass (both $P < 0.001$) and ECW-to-ICW ratio (early OA, $P = 0.034$; advanced OA, $P = 0.015$) were significantly associated with knee extension strength.

Conclusion. Lower-limb muscle quality was associated with knee extension strength, and the association was stronger in patients with knee OA. These findings suggest that both muscle quantity and quality should be assessed to better understand muscle function in patients with knee OA.

INTRODUCTION

Knee osteoarthritis (OA) is one of the most common musculoskeletal diseases in older people and is associated with physical dysfunction.¹ In particular, the loss of quadriceps strength is a

typical dysfunction in patients with knee OA^{2–4} and a critical factor for this condition because quadriceps weakness is related to the exacerbation of knee pain and restriction of activities of daily living.^{5–7} It is widely known that the quadriceps muscle loses muscle quantity and muscle quality caused by increased

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SIGNIFICANCE & INNOVATIONS

- This is the first study to show that the strength of the association between muscle composition (assessed by bioelectric impedance analysis) and knee extension strength varies with respect to the severity of knee osteoarthritis (OA).
- Lower-limb muscle quality, assessed using the extracellular-to-intracellular water ratio, was associated with knee extension strength, and this association was stronger in patients with knee OA.
- The association between lower-limb muscle quality and knee extension strength is already detected at the early stage of knee OA.
- These findings suggest that clinicians should assess not only muscle quantity but also muscle quality to maintain and improve muscle function in patients with knee OA.

noncontracted tissue,^{8,9} and these two changes are known to independently relate with muscle weakness.^{3,10} In particular, poor muscle quality, but not reduced quantity, impacts knee OA progression.¹¹ Therefore, quadriceps muscle quality is important in preventing the occurrence and progression of knee OA.

Intramuscular fat ratio, measured by using magnetic resonance imaging (MRI), is established as the gold standard for assessing muscle quality.¹² However, it is not widely used because of limited access or high cost. Bioelectric impedance analysis (BIA) is a noninvasive, easily available alternative to MRI.^{13,14} Although BIA is less accurate than MRI because it uses indirect assessment using differences in electrical resistance between various tissues,¹⁴ it reliably quantifies intracellular water (ICW) (representing contractive tissue or muscle mass) and extracellular water (ECW) (representing noncontractive tissue, such as adipose tissue). Because BIA can assess the proportion of noncontractive tissue in muscle via the ECW-to-ICW ratio, muscle mass and the ECW-to-ICW ratio can be evaluated as indicators of muscle quantity and quality, respectively. An elevated ECW value implies increased noncontractile tissue; therefore, an increase in the ECW-to-ICW ratio indicates lowered muscle quality.¹⁵

Recent evidence suggests that an elevated ECW-to-ICW ratio is associated with physical dysfunction.^{16–18} Older adults with lower-limb dysfunction, such as muscle weakness or decline in physical performance, display enhanced ECW-to-ICW ratios.¹⁶ In addition, patients with knee OA had higher ECW-to-ICW ratios than healthy older adults, and this was associated with reduced knee function.^{17,18} However, it is unclear whether the lowered muscle quality assessed by the ECW-to-ICW ratio was associated with muscle strength in patients with knee OA. Previously, we have reported the negative correlation between the ECW-to-ICW ratio and knee extension strength in community-dwelling older adults.¹⁹ However, we did not evaluate the severity of

radiographic knee OA and knee pain, and it was unclear how many of the included participants were patients with knee OA in that study. To our knowledge, there have been no studies relating muscle quality assessed by the ECW-to-ICW ratio to muscle strength and the severity of knee OA. It is necessary to determine the importance of muscle quality for muscle strength in patients with knee OA.

We assessed whether lower-limb muscle quantity and quality (assessed by BIA) are associated with knee extension strength and knee OA severity. We hypothesized that both lower-limb muscle quantity and quality were independently associated with knee extension strength and that muscle quality was strongly associated with muscle strength in patients with knee OA compared to healthy controls.

MATERIALS AND METHODS

Participants. The participants of this study were recruited from the Nagahama Prospective Cohort for Comprehensive Human Bioscience (the Nagahama Study). All participants were the general Japanese population of Nagahama City, which comprises around 115,000 inhabitants located in the Shiga Prefecture in Japan. Details of this cohort have been described in a previous study.¹⁷ Among 5,018 individuals who participated in the Nagahama Study and who were more than 60 years old, 3,270 individuals were included in our study. The sole inclusion criterion was knee OA severity assessed via Kellgren-Lawrence (KL) grading by orthopedic surgeons. Of these participants, we excluded 1,745 individuals based on the following exclusion criteria: (1) muscle strength was not measured; (2) the knee OA severity as measured by the KL classification was more advanced on the left side than on the right side (because muscle strength was evaluated only on the right leg); and (3) the patient was diagnosed with rheumatoid disease, central or peripheral neuropathy, chronic kidney disease, or chronic obstructive pulmonary disease. Finally, 1,525 individuals were included in our analysis (Figure 1). This study received the approval from the Ethics Committee of the Kyoto University Graduate School of Medicine and the Nagahama Municipal Review Board (G278) and was conducted in accordance with the Declaration of Helsinki. All participants were informed about the Nagahama Study, and their written consent was obtained for using their medical data.

Radiographic assessment of knee OA severity and knee symptoms. Radiographic assessment of knee OA severity was conducted by orthopedic surgeons who were not authors of this study. The anteroposterior diagnostic radiographic images were obtained while participants stood with both knees in full extension.

The symptoms section of the Knee Society Score (KSS) symptom score was used to assess knee symptoms.²⁰ This index consisted of three questions about knee pain during

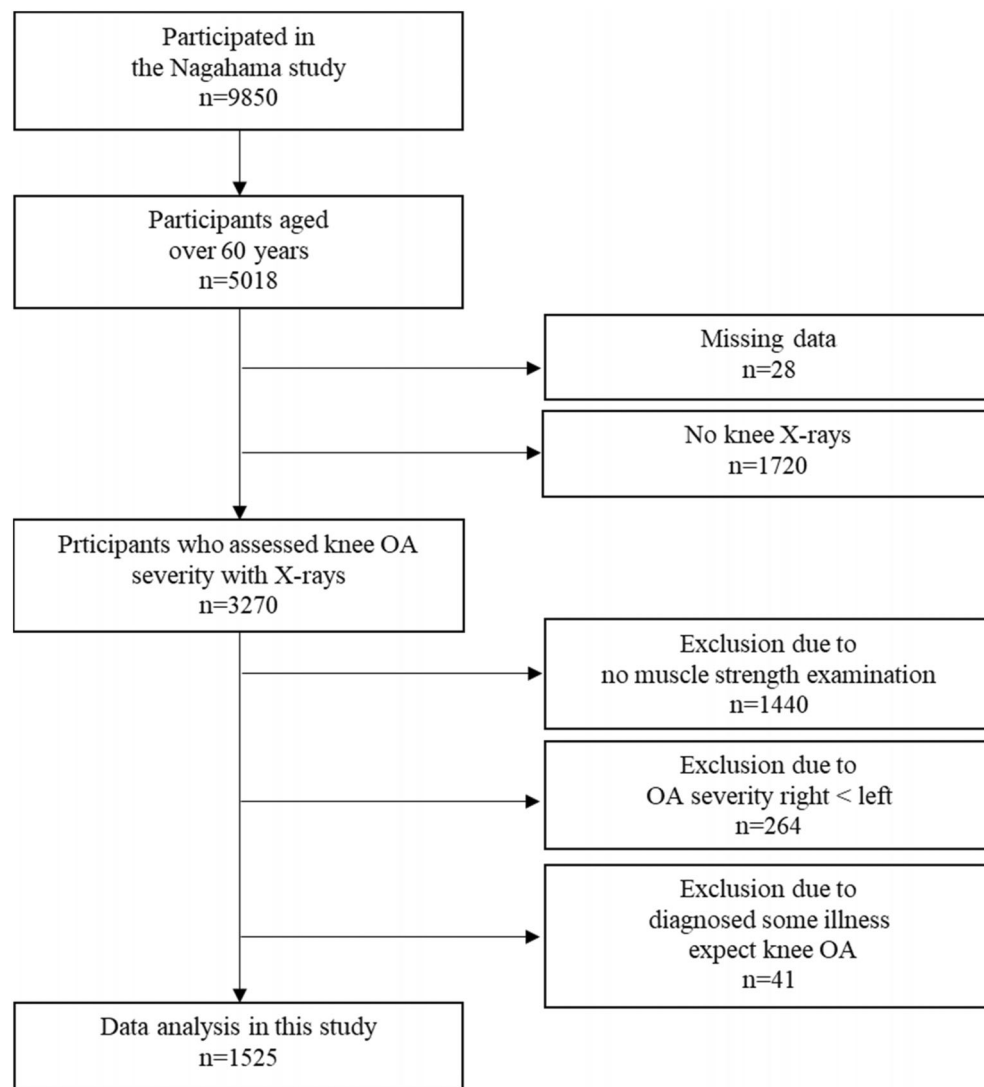


Figure 1. Flowchart of the selection of participants in this study. The flowchart shows the extraction of participants from the database of the Nagahama Study. OA, osteoarthritis.

walking and going up and down stairs and knee stiffness. The score ranges from 0 to 25, and a lower score indicates severe pain and stiffness of the knee. Based on a previous study,¹⁷ we classified the participants into three categories based on the degree of knee symptoms in the right knee as follows: asymptomatic (KSS symptom score ≥ 23), moderate (KSS symptom score ≥ 18), and severe (KSS symptom score < 18).

Evaluation of muscle strength. Knee extension strength in the right leg was measured during maximum voluntary isometric contraction using a dynamometer (Musculater; OG Giiken). Participants were seated on a dynamometer with the knee and hip joint at 90° flexion and performed knee extension with maximum effort. The measurement was taken twice after practicing several times. Each measured force value (N) was converted into torque (Nm), which was computed by multiplying it with the arm

length of shank. The higher value of the two measurements was used for analysis. Because the statistical analysis was performed using multiple linear regression adjusted for body mass index (BMI), it was not normalized by body mass.

Evaluation of body composition. Muscle quantity and quality in the right lower limb were assessed using a BIA device (InBody 430; InBody Co). Previous studies have confirmed the validity and repeatability of body compositional evaluation by BIA analysis in comparison to that measured by dual-energy x-ray absorptiometry and hydrostatic weighing.^{21–25} All participants were directed to refrain from consuming excessive amounts of water and overexercising before the measurement and were measured after a rest period to stabilize the hydration status in the whole body. Muscle quantity was calculated as the lower-limb muscle mass by using the BIA device automatically and obtaining

Table 1. Participants' characteristics*

	All (N = 1,525)	Control (n = 621)	Early OA (n = 402)	Advanced OA (n = 502)
Age, mean (SD), y	68.0 (5.3)	67.3 (5.2)	67.8 (5.4)	69.0 (5.3)
Female, n (%)	970 (64)	349 (56)	214 (53)	407 (81)
BMI, mean (SD)	22.3 (3.0)	21.8 (2.7)	22.2 (3.0)	23.1 (3.2)
KSS symptom score, mean (SD)	21.5 (4.6)	24.5 (0.8)	18.6 (4.0)	20.0 (5.4)
Knee extension strength, mean (SD), Nm	118.1 (51.2)	124.4 (54.5)	122.4 (51.7)	106.8 (44.4)
Lower-limb muscle mass, mean (SD), kg	6.3 (1.6)	6.4 (1.4)	6.5 (1.4)	6.0 (1.2)
Lower-limb ECW-to-ICW ratio, mean (SD), a.u.	4.9 (0.8)	4.7 (0.7)	4.8 (0.8)	5.1 (0.8)

* a.u., arbitrary unit; BMI, body mass index; ECW, extracellular water; ICW, intracellular water; KSS, Knee Society Score; OA, osteoarthritis.

a value that was confined to the right lower limb. To ascertain muscle quality, we calculated the ECW-to-ICW ratio in the right lower limb. ECW and ICW represent the amount of noncontractive (such as adipose tissue) and contractive elements of muscle, respectively. Thus, a higher ECW-to-ICW ratio indicates the relative increase of noncontractive elements in skeletal muscle, that is, the degeneration of muscle quality. The resistance values of frequencies of 5 kHz (Z_5) and 250 kHz (Z_{250}) were input into an algorithm to calculate the ECW-to-ICW ratio. The impedance for ECW was calculated as $(\text{body height})^2/Z_5$. As for the impedance for ICW, we calculated the difference between Z_{250} and Z_5 ($Z_{250} - 5$) as $1/([1/Z_{250}] - [1/Z_5])$, and the impedance for ICW was calculated as $(\text{body height})^2/(Z_{250} - 5)$. Lastly, the ECW-to-ICW ratio was calculated by dividing the impedance of the ECW compartment by that of the ICW compartment.^{17,26,27}

Statistical analysis. For our primary analysis, we investigated the association of muscle quantity and quality with knee extension strength. We conducted multiple linear regression analyses, with knee extension strength as a dependent variable; lower-limb muscle mass and the ECW-to-ICW ratio as independent variables; and age, sex, BMI, knee symptoms, and KL grade as adjustment variables.

For our secondary analysis, we examined whether the association of muscle quantity and quality with knee extension strength differed with knee OA severity. Participants were classified into three groups by employing KL grade and severity of knee symptoms. For the control group, the KL grade ranged from 0 to 1,

and the severity of knee symptoms was asymptomatic. For the early OA group, the KL grade ranged from 0 to 1, and the severity of knee symptoms was moderate to severe. For the advanced OA group, the KL grade ranged from 2 to 4. A multiple linear regression analysis was repeated for each of the three subgroups classified on the basis of OA severity and symptoms. All statistical analyses were conducted with IBM SPSS Statistics 22 software (IBM SPSS). The significance level of all analyses was set to $P < 0.05$.

RESULTS

Table 1 shows the general characteristics of the participants. After classification of the participants into three groups, the control group included 621 individuals (KL 0: $n = 51$ [8.2%]; KL 1: $n = 570$ [91.8%]), the early OA group included 402 individuals (KL 0: $n = 15$ [3.7%]; KL 1: $n = 387$ [96.3%]), and the advanced OA group included 502 individuals (KL 2: $n = 391$ [77.9%]; KL 3: $n = 102$ [20.3%]; KL 4: $n = 9$ [1.8%]).

From the primary analysis of all participants, our results showed that muscle mass (regression coefficient [B] = 23.44, 95% confidence interval [CI] 21.01–25.86, $P < 0.001$) and the ECW-to-ICW ratio (B = -3.73, 95% CI -6.50 to -0.95, $P = 0.009$) were significantly associated with knee extension strength (Table 2). From our secondary analysis for each subgroup, the lower-limb muscle mass was significantly associated with knee extension strength (B = 25.11, 95% CI 20.91–29.31, $P < 0.001$), but there was no association between the ECW-

Table 2. Association with muscle quality and quantity on knee extension strength in primary analysis*

	Association with knee extension strength			
	Unstandardized regression coefficient (B)	Standardized regression coefficient (β)	95% CI	P value
Lower-limb muscle mass	23.44	0.62	21.01 to 25.86	<0.001
Lower-limb ECW-to-ICW ratio	-3.73	-0.06	-6.50 to -0.95	0.009
Age	-0.76	-0.08	-1.15 to -0.37	<0.001
Sex	-14.27	-0.13	-21.22 to -7.31	<0.001
BMI	-0.90	-0.05	-1.58 to -0.23	0.009
Knee symptom severity	-2.76	-0.04	-5.21 to -0.30	0.028
KL grade	1.51	0.02	-1.26 to 4.29	0.285

* The results of multiple linear regression analysis included all participants. BMI, body mass index; CI, confidence interval; ECW, extracellular water; ICW, intracellular water; KL, Kellgren-Lawrence.

to-ICW ratio and knee extension strength ($B = -0.90$, 95% CI -6.05 to 4.25 , $P = 0.731$) in the control group. In the early OA group and the advanced OA group, the lower-limb muscle mass (early OA: $B = 25.66$, 95% CI 21.18 – 30.14 , $P < 0.001$; advanced OA: $B = 19.66$, 95% CI 15.80 – 23.51 , $P < 0.001$) and the ECW-to-ICW ratio (early OA: $B = -5.65$, 95% CI -10.88 to -0.42 , $P = 0.034$; advanced OA: $B = -5.07$, 95% CI -9.13 to -1.01 , $P = 0.015$) were significantly associated with knee extension strength (Table 3).

DISCUSSION

This is the first study to show that the strength of the association between muscle composition (assessed by BIA) and knee extension strength varies with respect to the severity of knee OA. As a result of our primary analysis, the loss of both muscle quantity and quality was observed to be independently associated with knee extension strength. In our secondary analysis, in which participants in the study cohort were classified into three groups based on the severity of knee OA, our results revealed differing trends in each group. Knee extension strength in patients with knee OA was associated with both muscle quantity and quality, but knee extension strength in healthy older adults was not associated with muscle quality. The results of our study suggest that an association between knee extension strength and lower-limb muscle quality arose only after the development of knee OA. This relationship was confirmed in the early stage of knee OA.

Our primary analysis indicated that lower-limb muscle quantity and quality were independently associated with knee extension strength. The associations were significant even after adjustment for the effects of sex, age, BMI, and knee symptom severity, which supported our hypothesis. A previous study using MRI found that the intramuscular fat ratio in the vastus medialis muscle was related to the loss of knee extension strength.²⁸ In addition, the ECW-to-ICW ratio assessed by segmental bioelectric impedance spectroscopy (S-BIS) was associated with a reduction in knee extension strength independently of quadriceps thickness measured via ultrasonographic images.¹⁹ Our findings

are in agreement with the results of previous reports. Yamada et al²⁹ discovered that the correlation between muscle mass and strength were strengthened when considering ECW assessed by S-BIS. In other words, muscle mass alone is inadequate to interpret muscle weakness because underestimating muscle atrophy may occur as a result of increased ECW estimates. This finding suggested that the proportion of contractive tissue decreased when the noncontractive tissue increased in muscle, and these changes were associated with muscle weakness. The most significant finding in this study is the significant association between lower-limb muscle quality and knee extension strength in patients with early and advanced knee OA. In patients with knee OA, the increased lower-limb ECW-to-ICW ratio is associated with a worsened KSS functional score.¹⁷ In addition, the quadriceps intramuscular fat ratios in patients with knee OA were higher than those in healthy controls, despite no significant loss in muscle mass, and were associated with knee dysfunction and severe symptoms.³⁰ A previous study has shown that aberrant collagen deposition in the extracellular matrix of muscle is detected despite the absence of muscle atrophy in the quadriceps muscle of patients with advanced knee OA compared to healthy controls³¹ and that their muscle cell degeneration is correlated with muscle weakness.³¹

Although the indicator evaluating muscle quality in our study differs from that in the study by Noehren et al,³¹ both indicators detect a relative increase of noncontractive tissue at the extracellular matrix of skeletal muscle. In addition, adipose tissue plays a role in inflammation resulting from arthritis, such as knee OA,³² and inflammatory cytokines emitted by adipose tissue have been suggested to be associated with worsened knee symptoms or muscle dysfunction.^{9,33} Although the relationship between muscle quality and muscle strength in knee OA has been unclear, it is possible that the effect of decreased muscle quality on muscle weakness is relatively stronger in patients with OA than in healthy controls. On the other hand, Fukumoto et al³⁴ reported that muscle quantity and quality were independently associated with knee extension strength in healthy community-dwelling older adults, and this is contradictory to our findings. Our study used the

Table 3. Association with muscle quality and quantity on knee extension strength for subgroups defined by knee OA severities and symptoms*

	Unstandardized regression coefficient (B)	Standardized regression coefficient (β)	95% CI	P value
Muscle mass				
Control group (n = 621)	25.11	0.65	20.91 to 29.31	<0.001
Early OA group (n = 402)	25.66	0.70	21.18 to 30.14	<0.001
Advanced OA group (n = 502)	19.66	0.52	15.80 to 23.51	<0.001
ECW-to-ICW ratio				
Control group (n = 621)	-0.90	-0.01	-6.05 to 4.25	0.731
Early OA group (n = 402)	-5.65	-0.09	-10.88 to -0.42	0.034
Advanced OA group (n = 502)	-5.07	-0.09	-9.13 to -1.01	0.015

* The multiple linear regression analysis was conducted in three subgroups. Each analysis was adjusted with age, sex, body mass index, and knee symptom severity. ECW-to-ICW ratio and muscle mass were shown as a representative of the results. CI, confidence interval; ECW, extracellular water; ICW, intracellular water; OA, osteoarthritis.

ECW-to-ICW ratio to assess muscle quality alteration, whereas the study by Fukumoto et al³⁴ used ultrasonographic echo intensity for this purpose. Although both a higher ECW-to-ICW ratio and an enhanced echo intensity are appropriate clinical signs of worsening muscle quality in patients with knee OA, it has been suggested that echo intensity is a more sensitive biomarker to detect muscle degeneration compared to the ECW-to-ICW ratio.¹⁸ Because BIA cannot evaluate individual muscles and echo intensity can achieve this goal, the specific degeneration of the quadriceps muscle may have been underestimated.

Although the muscle quality decline caused by aging may occur earlier than muscle atrophy,³⁵ the present study results suggest that the association between muscle quality and muscle strength in healthy older adults could not be detected because of the technical limitations of BIA. Alternatively, the community-dwelling older adults in the study by Fukumoto et al³⁴ may have included patients with potential knee OA because the assessment of knee OA severity using radiographic images was not conducted for them. These differing results depend on the measuring devices employed or the recruitment criteria applied and may possibly affect the discrepancy seen with previous studies. Our results clearly indicate that muscle weakness in patients with knee OA is associated with lower-limb muscle quality in addition to muscle quantity, and this relationship is already detectable in the early stage of knee OA. In terms of clinical implications, this study suggests that clinicians should conduct assessments early in the disease progression timeline by focusing on factors that can worsen muscle quality to maintain and improve muscle function in patients with knee OA.

Our study has several limitations. First, we could not clarify the association of muscle quantity and quality in the quadriceps muscle alone with knee extension strength because the muscle quantity and quality values determined by BIA cannot be specified for a particular muscle. Second, there may have been selection bias in the extraction of participants. The participation in the measurement of knee extension strength was voluntary in the Nagahama Study. Finally, the causal relationship between muscle weakness and increased ECW-to-ICW ratios in patients with knee OA remained unclear. Therefore, additional longitudinal research is needed in the future for better understanding these issues.

In conclusion, the lower-limb muscle quality assessed by the ECW-to-ICW ratio is associated with knee extension strength in patients with knee OA. In addition, this association is already detectable in the early stage of knee OA. These findings suggest that clinicians should assess not only muscle quantity but also muscle quality to maintain and improve muscle function in patients with knee OA.

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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 Taniguchi 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/Declaration of Helsinki requirements.

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