Enhanced echo intensity in vastus medialis is associated with worsening of functional disabilities and symptoms in patients with knee osteoarthritis: a 3-year longitudinal study

Introduction

Knee extensor weakness is one of the known risk factors for the worsening of functional disabilities and symptoms in patients with knee osteoarthritis (OA) [1, 2]; further, quadriceps muscle degeneration, such as muscle atrophy and fatty infiltration, is associated with knee extensor weakness [3]. Previously, a significant association of knee extensor weakness in patients with KOA was shown with increased intramuscular fat rather than muscle atrophy [4, 5], suggesting that the fatty infiltration of the quadriceps muscle should be evaluated to predict the worsening of functional disabilities and symptoms in patients with KOA.

Few previous studies [6-8] have indicated that the vastus medialis (VM) muscle degeneration is associated with future cartilage loss. Wang et al. [6] showed that the cross-sectional area (CSA) of the VM was negatively associated with cartilage volume loss and worsening symptoms over a period of two years. Another study [7] indicated that an increase in VM fat content was related to cartilage loss but not to worsening knee symptoms. Further, a recent study [8] also suggested that the greater quadriceps fatty infiltration, specifically in the VM, was associated with cartilage loss. All these findings indicate a possible association between VM muscle degeneration and the progression of KOA. Since the radiographic severity is not necessarily related to functional disability and symptoms in KOA [9], assessment of VM muscle degeneration may provide an important tool for predicting the worsening of functional disabilities and symptoms.

In the studies mentioned above, the muscle quantity and quality were assessed using magnetic resonance imaging (MRI); however, the application of MRI can be complicated in clinical settings due to associated issues such as unavailability, operating time, and cost. Ultrasound imaging and segmental-bioelectrical impedance spectroscopy (S-BIS) are useful and convenient alternative methods to assess muscle quantity and quality. Muscle thickness (MT) evaluation via ultrasound imaging is a common index that reflects muscle mass [10]. Muscle echo intensity (EI) using ultrasound images and extracellular-to-intracellular water (ECW/ICW) ratio using S-BIS are known as muscle quality indices [3, 11, 12]. Enhanced EI and higher ECW/ICW ratio reflect a relative increase in non-contractile tissue to muscle mass, including increased fatty infiltration [11, 13]. Taniguchi et al. [14] showed that increased VM-EI and a higher ECW/ICW ratio, rather than VM-MT, characterized quadriceps muscle degeneration in patients with KOA.

Furthermore, the ECW/ICW ratio is associated with functional disabilities and severe knee pain in patients with KOA [15]. Therefore, muscle quality measured using ultrasound images and S-BIS may infer the worsening of functional disabilities and symptoms in patients with KOA. However, to our knowledge, no longitudinal study has investigated such associations.

This study aimed to clarify the association between muscle degeneration at baseline and the worsening of functional disabilities and symptoms in patients with KOA over a period of 3 years. We hypothesized that increased VM-EI and a higher ECW/ICW ratio at baseline are associated with worsening functional disabilities and symptoms in patients with KOA.

Methods

Patients

In this prospective cohort study, female outpatients aged ≥60 years with KOA were recruited from the Department of Orthopaedic Surgery at the Kobayashi Hospital, Japan, between September and December 2018. All patients were diagnosed based on the American College of Rheumatology criteria for KOA [16], and OA severity was assessed using the Kellgren−Lawrence (KL) grading system [17]. The inclusion criteria were as follows: (1) diagnosis of symptomatic and medial KOA, (2) ability to live independently, and (3) ability to walk without any assistive device in daily life. The exclusion criteria were as follows: (1) history of surgery for the back or both limbs, (2) diagnosis of rheumatoid arthritis and osteonecrosis of the knee, and (3) cardiovascular or neurological disorders. A total of 47 patients (mean age, 71.1±6.3 years) were eligible for this study and underwent baseline measurements. As the definition of which side of the knee is targeted for measurement in patients with bilateral KOA, the side with more severe radiographic OA was selected for baseline measurement. Additionally, if the patient had equal radiographic OA severity in both the knees, the more painful side was selected for analysis. The follow-up data were collected from August to November 2021 at the Kobayashi Hospital. During the follow-up period, three patients were excluded due to total knee arthroplasty, two were excluded due to fractures (femoral neck and lumbar compression fractures), and one case was excluded owing to the need for cancer treatment. Eight patients were lost to follow-up, including those who refused to participate due to the COVID-19 pandemic. Finally, of the 47 patients at baseline, 33 with KOA were included in the data analysis.

All patients were informed of the aim and procedures of the study, and all the patients provided written informed consent before participation. All study procedures were approved by the Ethics Committee of the Kyoto University Graduate School of Medicine and conducted according to the principles of the Declaration of Helsinki.

Self-reported knee function and symptoms

Knee functional disabilities and symptoms were assessed using the Knee Society Knee Scoring System (KSS) 2011 Japanese Edition. The KSS is a self-reported assessment tool, and its validity has been shown in the Japanese population [18]. Of the four KSS subcategories (symptoms, satisfaction, expectations, and functional activities), functional activities and symptom categories were used in this study. The functional activities category consisted of four components: walking and standing, routine activities, advanced activities, and discretionary activities. Function scores (0−100 points) evaluate the degree of physical dysfunction during daily activities, with lower scores representing worse functional activity. The symptom category consisted of three components: the degree of knee pain during walking, the degree of knee pain when travelling up or down stairs, and knee stiffness. The maximum possible symptom score was 25 points, with lower scores representing the worse knee symptoms.

To assess changes in KSS function and symptom scores, patients answered the KSS questionnaire at baseline and 3 years later. Based on a previous report [19] regarding the minimum clinically important difference (MCID) for the KSS function and symptom scores, this study defined a reduction of more than -4.1 points in KSS function or -1.9 points in KSS symptom as the presence of functional disabilities and/or symptoms progression. If either the KSS function or symptom scores had a reduction greater than the MCID scores, the patient was classified into the progressive group.

Radiographic* *KOA* *assessment

For radiographic assessment of the knees, anteroposterior weight-bearing views were obtained when the patients stood in a knee flexion position [20]; this method provides more stability than the fully extended position used in the Rosenberg method. Mild and severe KOA were defined as the KL grade of 2 and ≥3, respectively, in one or both the knees.

Measurement of knee extensor strength

The patients were seated on a dynamometer (Isoforce GT-330; OG GIKEN Co., Okayama, Japan) with the knee joint at 60° flexion. Knee extensor strength was measured twice for approximately 3 s after familiarization with maximum muscle contraction, and a greater force (N) was obtained. The maximal torque (Nm) was calculated by multiplying the force (N) and lever arm (m).

MT and EI measurements using ultrasound images

As both decreased MT and enhanced EI are independently associated with loss of muscle strength, MT and EI are widely used for muscle quantity and quality indices [3, 21, 22]. Transverse B-mode ultrasound images were obtained using an ultrasound imaging device (LOGIQ e; GE Healthcare UK Ltd., Chalfont, UK) with an 8 MHz linear-array probe. After the patients rested in the supine position on the bed for more than 3 min, the same investigator measured the transverse ultrasound image of the VM 30% distal between the greater trochanter and lateral femoral tuberosity [23]. The settings of the ultrasound device were unified; the gain was 58 dB, the dynamic range was 69 dB, and the focus depth was the middle of the VM. VM-MT was measured as the distance between the muscle fasciae and femoral bone. The mean EI of the VM was obtained by converting the image pixels to an 8-bit grayscale using image analysis software (ImageJ-WinJP; LISIT, Japan; Fig. 1) and expressed as a 256-point value from 0 (black) to 255 (white). The enhanced EI is associated with increased non-contractile tissue within the muscle, including fat tissue investigated by muscle biopsy [13, 24]. The EI analyses of VM were performed by another investigator blinded to the clinical data. The high reliability of the MT and EI measurements by an investigator who measured the ultrasound images was confirmed and has been reported in our previous study [14].

The measurement of ECW/ICW ratio using S-BIS

S-BIS measurement of the upper thigh was performed following ultrasound measurement to avoid the immediate effect of body water redistribution. Bioelectrical impedance was obtained from multi-frequency S-BIS equipment (SFB7, ImpediMed Inc., Australia) with a logarithmic spectrum of 256 frequencies ranging from 4–1000 kHz using disposable tab-type electrodes (Red Dot TM; 3M Inc., Japan). S-BIS measurements were taken for approximately 3 s to acquire bioelectrical impedances and were repeated three times consecutively. Data processing was performed using the SFB7 software (Bioimp software, ImpediMed Inc., Australia). The resistances of zero (R_0) and infinity (R_∞) were obtained by fitting the spectrum of the impedance data to the Cole-Cole model. R_0 represents the ECW compartment, and R_∞ represents the total body water compartment (TBW; i.e., $R_\infty = R_{TBW}$). The resistance of the ICW compartment (R_{ICW}) was calculated as $1/[(1/R_{TBW)} – (1/R_{ECW})]$. ECW and ICW were estimated by applying the calculation algorithm used in previous studies [11, 14]. The calculation equations of ICW and ECW are described as follows: $ECW = \rho_{ECW} \times length^2 / R_{ECW}$ and $ICW = \rho_{ICW} \times length^2 / R_{ICW}$, where ρ indicates the segment-specific extracellular resistivity ($\rho_{ECW} = 47$ Ωcm) and intracellular resistivity ($\rho_{ICW} = 273.9$ Ωm). The segment length (cm) was determined and measured as the distance between the anterior superior iliac spine and the proximal end of the patella. After obtaining the ECW and ICW values, the ECW/ICW ratio was calculated as ECW against ICW. The high reliability of the S-BIS measurement was confirmed in our previous study [14].

Statistical analysis

SPSS software (version 25.0; SPSS Japan Inc., Tokyo, Japan) was used for all the statistical tests. Statistical significance was set at $p < 0.05$. All baseline values are shown as the mean and standard deviation. Univariate and multivariate logistic regression analyses were used to identify the predictors for classification into the progressive group. As the dependent variable was the group (reference, no progressive group = 0; progressive group = 1), univariate logistic regression was conducted to estimate the odds ratio (OR) and accompanying 95% confidence interval (CI) for each parameter at baseline. In addition, multivariable logistic regression analysis was conducted with adjustment variables, including age, body mass index (BMI), and radiographic OA severity.

Furthermore, we performed multivariable logistic regression analysis for each subcategory (worsening of functional disabilities; worsening of symptoms) to identify the association between muscle degeneration at baseline and future progression in patients with KOA. Multivariable logistic regression analysis with the forced entry method was conducted with the presence of functional disability progression as the dependent variable and VM-MT, VM-EI, and ECW/ICW ratio at baseline as independent variables, including the age, BMI, radiographic OA severity, and baseline KSS function score as potential confounders. Similarly, multiple logistic regression analysis for the presence of symptom progression was also performed, adjusting for baseline KSS symptom scores as covariates.

Results

Table 1 shows the baseline characteristics of the patients with KOA who completed 3 years of follow-up. Of the 33 patients with a significant change in KSS function or symptom score, 13 (39.4%) were classified into the progressive group; 10, 2, and 1 had functional disability and symptom, functional disability, and symptom progressions, respectively.

In the univariable logistic regression analysis (Table 2), a higher KSS function score at baseline was significantly associated with progression (crude OR [95% CI], 1.07 [1.01−1.13], $p = 0.032$); however, the knee extensor strength at baseline showed non-significant association (crude OR [95% CI], 1.02 [0.99–1.05], $p = 0.252$). In muscle degeneration indicators, the enhanced VM-EI (crude OR [95% CI], 1.10 [1.01−1.20], $p = 0.023$) was identified as a potential predictor of progression. In the multivariable analysis, enhanced VM-EI was the only significant predictor of progression (adjusted OR [95% CI], 1.13 [1.03−1.25], $p = 0.014$) (Table 2).

In the logistic regression subcategory analysis, the VM-EI, but not the VM-MT and ECW/ICW ratio, at baseline was found to be significantly associated with the progression of functional disabilities (adjusted OR [95% CI], 1.24 [1.03−1.50], $p = 0.024$) and symptoms (adjusted OR [95% CI], 1.13 [1.01−1.25], $p = 0.029$) even after adjustment for baseline KSS scores (Table 3).

Discussion

This is the first longitudinal study to define the association of muscle degeneration at baseline with the progression of functional disabilities and symptoms in patients with KOA, focusing on muscle quality evaluated by the VM-EI and ECW/ICW ratio parameters. The most important finding of the present study was that VM-EI at baseline was a significant independent predictor of functional disability and symptom progression in patients with KOA. This finding partially supports our hypothesis that the enhanced VM-EI (loss of muscle quality) in KOA patients is associated with the future worsening of functional disabilities and symptoms.

According to the results of multivariable logistic regression, VM-EI was selected as a predictor of the progression group but not the knee extensor strength. Although knee extensor weakness is generally associated with functional disabilities and symptoms in cross-sectional studies [1, 2], a previous meta-analysis [25] indicated that knee extensor strength could not predict KOA progression. Although knee extensor weakness is affected by pain during muscle strength testing [26], imaging devices' assessment of muscle function is pain-independent. A previous study [25] and our results suggest that the knee extensor weakness at baseline is unsuitable for future predictions of functional disabilities and symptoms. Additionally, consistent with a previous study [8] that investigated the CSA of the quadriceps muscle using MRI, the VM-MT was also not a predictor of future worsening of functional disabilities and symptom progression. Regions of interest for evaluating muscle mass from images contain non-contractile elements, including fat and fibrous tissues. Thus, there is an issue that the actual muscle contraction element is overestimated when the non-contractile element increases within the muscle [27-29]. This potential effect may have been the reason why the indicator of muscle mass was not associated with future functional disabilities or symptom worsening in patients with KOA.

Consistent with our hypotheses, VM-EI at baseline was associated with functional disabilities and symptom progression in patients with KOA over 3 years. To our knowledge, this study is the first to longitudinally confirm these associations, although a previous cross-sectional study [30] reported that intramuscular fat infiltration of VM, which was measured using a chemical shift-based water-fat separation MRI method, was related to functional disabilities and symptoms. Clinically, it is a strong point that EI determined via ultrasound imaging can act as an alternative index in addition to the intramuscular fat infiltration determination using MRI to predict the future progression of disabilities and symptoms in patients with KOA. Some histochemical studies [31, 32] have shown an increase in non-contractile tissue within the VM on muscle biopsy, but this increase is not fully known. Arthrogenic muscle inhibition is one possible mechanism [33]. According to this theory, muscle and joint damage inflammation is linked to neural inhibition in the quadriceps [34, 35]. VM degeneration, which anatomically attaches closest to the painful site, could be sensitively associated with KOA-related functional disabilities and symptom changes.

Contrary to our hypothesis, the ECW/ICW ratio was not a predictive factor for functional disabilities and symptoms over 3 years of follow-up. A previous study [14] has suggested that the VM-EI is more accurate than ECW/ICW ratio in distinguishing between the OA and healthy knees, although they both characterize muscle degeneration in patients with KOA compared to the healthy subjects. While the VM-EI evaluates the muscle quality within individual muscles, the ECW/ICW ratio cannot distinguish the VM muscle from the quadriceps. Although a population-based cross-sectional study [15] has shown that the ECW/ICW ratio is associated with functional disability in KOA patients, our results suggest that the ECW/ICW ratio is not sensitive to predicting longitudinal changes. Thus, the VM-EI than the ECW/ICW ratio was a robust assessment tool for detecting worsened functional disabilities and symptoms in longitudinal changes.

MRI has the advantage of its highly accurate analysis, but the disadvantage is the time cost of imaging operation and analysis. On the other hand, ultrasound imaging is a low-cost and convenient method, and EI via ultrasound imaging reflects intramuscular fat measured by MRI [36]. Thus, the measurement of EI using ultrasound imaging is recommended to evaluate muscle quality in clinical settings. Additionally, our findings suggest that the rheumatologist can assess the risk of future worsening functional disabilities and symptoms by measuring the VM-EI in primary care.

This study had some limitations. First, the sample size of patients who completed the follow-up over 3 years was small. In addition, the participants of this study were all female patients with KOA; thus, caution should be exercised when generalizing the results. Second, each patient's medical management and lifestyle during the follow-up period could not be assessed. Therefore, confounding factors may have affected the study results. Furthermore, since no age-matched healthy control group was set in the current study, it was unclear whether our findings were specific to KOA. Future studies must clarify whether the worsening of functional disabilities and symptoms with the enhanced VM-EI is due to age-related or disease-specific KOA changes.

In conclusion, the current study's findings suggest that the enhanced VM-EI was associated with worsening functional disabilities and symptoms in patients with KOA over 3 years. VM-EI, which can be easily determined using the ultrasound images in clinical settings, may be useful for predicting future dysfunction and symptomatic worsening in patients with KOA.

Declarations

Compliance with ethical standards

All study procedures were approved by the Ethics Committee of the Kyoto University Graduate School of Medicine and conducted in accordance with the principles of the Declaration of Helsinki (protocol identification number R1647). All patients were informed of the aim and procedures of the study, and all the patients provided written informed consent before participation.

Funding

This study was supported by JSPS KAKENHI Grant-in-Aid for Scientific Research (18H03164 and 20K19376). This grant was used for data collection, data analysis, and manuscript writing.

Authors' contributions

All authors have made substantial contributions to (1) the conception and design of the study, (2) revising it critically for important intellectual content, and (3) final approval of the version to be submitted. The specific contributions of each author are as follows.

(1) Analysis and interpretation of data: MT, YF, MY, and NI.

(2) Article drafting: MT, YF, MY, and NI.

Data availability

The surveys and material are available upon reasonable request to the corresponding author.

Acknowledgements

We would like to thank Editage (www.editage.jp) for English language editing.

References

1. Ruhdorfer A, Wirth W, Eckstein F (2015) Relationship between isometric thigh muscle strength and minimum clinically important differences in knee function in osteoarthritis: data from the osteoarthritis initiative. Arthritis Care Res (Hoboken) 67:509-518. https://doi.org/10.1002/acr.22488

2. Ruhdorfer A, Wirth W, Eckstein F (2017) Association of knee pain with a reduction in thigh muscle strength - a cross-sectional analysis including 4553 osteoarthritis initiative participants. Osteoarthritis Cartilage 25:658-666. https://doi.org/10.1016/j.joca.2016.10.026

3. Fukumoto Y, Ikezoe T, Yamada Y, Tsukagoshi R, Nakamura M, Mori N, Kimura M, Ichihashi N (2012) Skeletal muscle quality assessed from echo intensity is associated with muscle strength of middle-aged and elderly persons. Eur J Appl Physiol 112:1519-1525.

https://doi.org/10.1007/s00421-011-2099-5

4. Maly MR, Calder KM, Macintyre NJ, Beattie KA (2013) Relationship of intermuscular fat volume in the thigh with knee extensor strength and physical performance in women at risk of or with knee osteoarthritis. Arthritis Care Res (Hoboken) 65:44-52. https://doi.org/10.1002/acr.21868

5. Pedroso MG, de Almeida AC, Aily JB, de Noronha M, Mattiello SM (2019) Fatty infiltration in the thigh muscles in knee osteoarthritis: a systematic review and meta-analysis. Rheumatol Int 39:627-635. https://doi.org/10.1007/s00296-019-04271-2

6. Wang Y, Wluka AE, Berry PA, Siew T, Teichtahl AJ, Urquhart DM, Lloyd DG, Jones G, Cicuttini FM (2012) Increase in vastus medialis cross-sectional area is associated with reduced pain, cartilage loss, and joint replacement risk in knee osteoarthritis. Arthritis Rheum 64:3917-3925. https://doi.org/10.1002/art.34681

7. Raynauld JP, Pelletier JP, Roubille C, Dorais M, Abram F, Li W, Wang Y, Fairley J, Cicuttini FM, Martel-Pelletier J (2015) Magnetic resonance imaging-assessed vastus medialis muscle fat content and risk for knee osteoarthritis progression: Relevance from a clinical trial. Arthritis Care Res (Hoboken) 67:1406-1415. https://doi.org/10.1002/acr.22590

8. Kumar D, Link TM, Jafarzadeh SR, LaValley MP, Majumdar S, Souza RB (2021) Association of quadriceps adiposity with an increase in knee cartilage, meniscus, or bone marrow lesions over three years. Arthritis Care Res (Hoboken) 73:1134-1139. https://doi.org/10.1002/acr.24232

9. Barker K, Lamb SE, Toye F, Jackson S, Barrington S (2004) Association between radiographic joint space narrowing, function, pain and muscle power in severe osteoarthritis of the knee. Clin Rehabil 18:793-800. https://doi.org/10.1191/0269215504cr754oa

10. Miyatani M, Kanehisa H, Kuno S, Nishijima T, Fukunaga T (2002) Validity of ultrasonograph muscle thickness measurements for estimating muscle volume of knee extensors in humans. Eur J Appl Physiol 86:203-208. https://doi.org/10.1007/s00421-001-0533-9

11. Yamada Y, Buehring B, Krueger D, Anderson RM, Schoeller DA, Binkley N (2017) Electrical properties assessed by segmental bioelectrical impedance spectroscopy as biomarkers of age-related loss of skeletal muscle quantity and quality. J Gerontol A Biol Sci Med Sci 72:1180-1186. https://doi.org/10.1093/gerona/glw225

12. Taniguchi M, Yamada Y, Fukumoto Y, Sawano S, Minami S, Ikezoe T, Watanabe Y, Kimura M, Ichihashi N (2017) Increase in echo intensity and extracellular-to-intracellular water ratio is independently associated with muscle weakness in elderly women. Eur J Appl Physiol 117:2001-2007. https://doi.org/10.1007/s00421-017-3686-x

13. Pillen S, Tak RO, Zwarts MJ, Lammens MM, Verrijp KN, Arts IM, van der Laak JA, Hoogerbrugge PM, van Engelen BG, Verrips A (2009) Skeletal muscle ultrasound: correlation between fibrous tissue and echo intensity. Ultrasound Med Biol 35:443-446. https://doi.org/10.1016/j.ultrasmedbio.2008.09.016

14. Taniguchi M, Fukumoto Y, Yagi M, Yamagata M, Kobayashi M, Yamada Y, Kimura M, Ichihashi N (2021) Enhanced echo intensity and a higher extracellular water-to-intracellular water ratio are helpful clinical signs for detecting muscle degeneration in patients with knee osteoarthritis. Clin Rheumatol 40:4207- 4215. https://doi.org/10.1007/s10067-021-05763-y

15. Taniguchi M, Ikezoe T, Kamitani T, Tsuboyama T, Ito H, Matsuda S, Tabara Y, Matsuda F, Ichihashi N, Nagahama Study G (2021) Extracellular-to-intracellular water ratios are associated with functional disability levels in patients with knee osteoarthritis: results from the Nagahama Study. Clin Rheumatol 40:2889-2896. https://doi.org/10.1007/s10067-021-05591-0

16. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, Christy W, Cooke TD, Greenwald R, Hochberg M, et al. (1986) Development of criteria for the classification and reporting of osteoarthritis: Classification of osteoarthritis of the knee Arthritis Rheum 29:1039-1049. https://doi.org/10.1002/art.1780290816

17. Kellgren JH, Lawrence JS (1957) Radiological assessment of osteo-arthrosis. Ann Rheum Dis 16:494-502. https://doi.org/10.1136/ard.16.4.494

18. Taniguchi N, Matsuda S, Kawaguchi T, Tabara Y, Ikezoe T, Tsuboyama T, Ichihashi N, Nakayama T, Matsuda F, Ito H (2015) The KSS 2011 reflects symptoms, physical activities, and radiographic grades in a Japanese population. Clin Orthop Relat Res 473:70-75. https://doi.org/10.1007/s11999-014-3650-6

19. Nishitani K, Yamamoto Y, Furu M, Kuriyama S, Nakamura S, Ito H, Fukuhara S, Matsuda S (2019) The minimum clinically important difference for the Japanese version of the new Knee Society Score (2011KSS) after total knee arthroplasty. J Orthop Sci 24:1053-1057. https://doi.org/10.1016/j.jos.2019.09.001

20. Kan H, Arai Y, Kobayashi M, Nakagawa S, Inoue H, Hino M, Komaki S, Ikoma K, Ueshima K, Fujiwara H, Yokota I, Kubo T (2017) Fixed-flexion view X-ray of the knee superior in detection and follow-up of knee osteoarthritis. Medicine 96:e9126. https://doi.org/10.1097/MD.0000000000009126

21. Rech A, Radaelli R, Goltz FR, da Rosa LH, Schneider CD, Pinto RS (2014) Echo intensity is negatively associated with functional capacity in older women. Age 36:9708. https://doi.org/10.1007/s11357-014-9708-2

22. Lopez P, Wilhelm EN, Rech A, Minozzo F, Radaelli R, Pinto RS (2017) Echo intensity independently predicts functionality in sedentary older men. Muscle Nerve 55:9-15. https://doi.org/10.1002/mus.25168

23. Maden-Wilkinson TM, Degens H, Jones DA, McPhee JS (2013) Comparison of MRI and DXA to measure muscle size and age-related atrophy in thigh muscles. J Musculoskelet Neuronal Interact 13:320-328

24. Reimers K, Reimers CD, Wagner S, Paetzke I, Pongratz DE (1993) Skeletal muscle sonography: a

correlative study of echogenicity and morphology. J Ultrasound Med 12:73-77

25. Bastick AN, Belo JN, Runhaar J, Bierma-Zeinstra SM (2015) What are the prognostic factors for radiographic progression of knee osteoarthritis? A meta-analysis. Clin Orthop Relat Res 473:2969-2989. https://doi.org/10.1007/s11999-015-4349-z

26. Henriksen M, Rosager S, Aaboe J, Graven-Nielsen T, Bliddal H (2011) Experimental knee pain reduces muscle strength. J Pain 12:460-467. https://doi.org/10.1016/j.jpain.2010.10.004

27. Goodpaster BH, Carlson CL, Visser M, Kelley DE, Scherzinger A, Harris TB, Stamm E, Newman AB (2001) Attenuation of skeletal muscle and strength in the elderly: The Health ABC Study. J Appl Physiol (1985) 90:2157-2165. https://doi.org/10.1152/jappl.2001.90.6.2157

28. Visser M, Kritchevsky SB, Goodpaster BH, Newman AB, Nevitt M, Stamm E, Harris TB (2002) Leg muscle mass and composition in relation to lower extremity performance in men and women aged 70 to 79: the health, aging and body composition study. J Am Geriatr Soc 50:897-904. https://doi.org/10.1046/j.1532-5415.2002.50217.x

29. Yamada Y, Schoeller DA, Nakamura E, Morimoto T, Kimura M, Oda S (2010) Extracellular water may mask actual muscle atrophy during aging. J Gerontol A Biol Sci Med Sci 65:510-516. https://doi.org/10.1093/gerona/glq001

30. Kumar D, Karampinos DC, Macleod TD, Lin W, Nardo L, Li X, Link TM, Majumdar S, Souza RB (2014) Quadriceps intramuscular fat fraction rather than muscle size is associated with knee

osteoarthritis. Osteoarthr Cartil 22:226-234. https://doi.org/10.1016/j.joca.2013.12.005

31. Fink B, Egl M, Singer J, Fuerst M, Bubenheim M, Neuen-Jacob E (2007) Morphologic changes in the vastus medialis muscle in patients with osteoarthritis of the knee. Arthritis Rheum 56:3626-3633. https://doi.org/10.1002/art.22960

32. Ikemoto-Uezumi M, Matsui Y, Hasegawa M, Fujita R, Kanayama Y, Uezumi A, Watanabe T, Harada A, Poole AR, Hashimoto N (2017) Disuse atrophy accompanied by intramuscular ectopic adipogenesis in vastus medialis muscle of advanced osteoarthritis patients. Am J Pathol 187:2674-2685. https://doi.org/10.1016/j.ajpath.2017.08.009

33. Rice DA, McNair PJ (2010) Quadriceps arthrogenic muscle inhibition: neural mechanisms and treatment perspectives. Semin Arthritis Rheum 40:250-266. https://doi.org/10.1016/j.semarthrit.2009.10.001

34. Levinger I, Levinger P, Trenerry MK, Feller JA, Bartlett JR, Bergman N, McKenna MJ, Cameron-Smith D (2011) Increased inflammatory cytokine expression in the vastus lateralis of patients with knee osteoarthritis. Arthritis Rheum 63:1343-1348. https://doi.org/10.1002/art.30287

35. Dalle S, Koppo K (2020) Is inflammatory signaling involved in disease-related muscle wasting? Evidence from osteoarthritis, chronic obstructive pulmonary disease and type II diabetes. Exp Gerontol 137:110964. https://doi.org/10.1016/j.exger.2020.110964

36. Fukumoto Y, Taniguchi M, Hirono T, Yagi M, Yamagata M, Nakai R, Asai T, Yamada Y, Kimura M,

Ichihashi N (2022) Influence of ultrasound focus depth on the association between echo intensity and intramuscular adipose tissue. Muscle Nerve. https://doi.org/10.1002/mus.27677

Table 1. Baseline characteristics of study participants

	All patients (n = 33)	No progression group (n = 20)	Progression group (n = 13)
Age, y	71.6 (5.3)	72.6 (4.8)	70.1 (5.7)
Body mass index, kg/m^2	24.5 (4.4)	25.7 (4.6)	22.7 (3.6)
Radiographic OA severities			
mild, KL = 2	16 (48.5 %)	8 (40.0 %)	8 (61.5 %)
severe, KL = 3 or 4	17 (51.5 %)	12 (60.0 %)	5 (38.5 %)
KSS function score, /100	68.8 (17.3)	63.2 (17.4)	77.5 (13.8)
KSS symptom score, /25	15.5 (5.9)	13.8 (5.7)	18.1 (5.4)
Knee extensor strength, Nm	65.2 (26.6)	60.7 (24.9)	71.8 (28.7)
Muscle thickness of vastus medialis, cm	1.76 (0.46)	1.83 (0.51)	1.66 (0.39)
Echo intensity of vastus medialis, a.u.	93.3 (12.1)	89.1 (11.3)	99.8 (10.5)
ECW/ICW ratio	0.43 (0.14)	0.43 (0.12)	0.43 (0.17)

Variables are presented as means (SDs) or *n* (%).

Abbreviations: OA, osteoarthritis; KL, Kellgren-Lawrence; KSS, knee society score; ECW/ICW, extracellular-to-intracellular water; a.u., arbitrary unit.

Table 2. Univariable and multivariable logistic regression analysis for predicting the presence of progression group

	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Age, y	0.91 (0.79 - 1.05)	0.192	—	
Body mass index, kg/m^2	0.83 (0.68 - 1.01)	0.067	—	
Radiographic OA severities, reference = mild	ref.			
severe	0.42 (0.10 - 1.74)	0.231	—	
KSS function score, /100	1.07 (1.01 - 1.13)	0.032	1.06 (0.97 - 1.15)	0.192
KSS symptom score, /100	1.15 (1.00 - 1.33)	0.050	1.19 (0.97 - 1.46)	0.099
Knee extensor strength, Nm	1.02 (0.99 - 1.05)	0.252	1.01 (0.97 - 1.05)	0.648
Muscle thickness of vastus medialis, cm	0.44 (0.09 - 2.16)	0.314	0.48 (0.05 - 4.77)	0.528
Echo intensity of vastus medialis, a.u.	1.10 (1.01 - 1.20)	0.023	1.13 (1.03 - 1.25)	0.014
ECW/ICW ratio	0.85 (0.01 - 143.6)	0.950	5.05 (0.01 - 4884.01)	0.644

Multivariable logistic regression analysis was conducted for the dependent variable of the progression/no-progression groups (reference, no progressive group = 0, [n = 20]; progressive group = 1, [n = 13]), with adjustment for the age, body mass index, and radiographic OA severity.

Abbreviations: OR, odds ratio; CI, confidence interval; OA, osteoarthritis; ECW/ICW, extracellular-to-intracellular water; a.u., arbitrary unit.

Table 3. Associations of muscle degeneration on worsening of functional disabilities and symptoms in patients with KOA

	OR (95% CI)	p-value
Worsening functional disabilities		
Muscle thickness of vastus medialis	0.90 (0.03 - 29.64)	0.954
Echo intensity of vastus medialis	1.24 (1.03 - 1.50)	0.024
ECW/ICW ratio	0.00 (0.00 - 22072.12)	0.480
Age	0.82 (0.60 - 1.13)	0.222
Body mass index	0.84 (0.55 - 1.28)	0.414
Radiographic OA severities	13.16 (0.42 - 416.19)	0.144
Baseline of KSS function	1.15 (0.99 - 1.32)	0.065
Worsening symptoms		
Muscle thickness of vastus medialis	0.46 (0.02 - 8.65)	0.601
Echo intensity of vastus medialis	1.13 (1.01 - 1.25)	0.029
ECW/ICW ratio	0.66 (0.00 - 2204.49)	0.920
Age	0.87 (0.68 - 1.11)	0.251
Body mass index	0.93 (0.71 - 1.23)	0.612
Radiographic OA severities	2.22 (0.18 - 26.90)	0.532
Baseline of KSS symptoms	1.21 (0.96 - 1.52)	0.110

Multivariable logistic regression analyses were performed for each subcategory (worsening of functional disabilities; worsening of symptoms). Logistic regression analyses were conducted with the group (reference, no-progression group = 0; progression group = 1) as the dependent variable and the VM-MT, VM-EI, and ECW/ICW ratio as independent variables with adjustment for the age, body mass index, radiographic OA severity, and baseline KSS scores.

Abbreviations: OR, odds ratio; CI, confidence interval; ECW/ICW, extracellular-to-intracellular water; OA, osteoarthritis; KSS, Knee Society Score.

Figure Caption

Fig. 1 Representative ultrasound images of the vastus medialis muscles in patients with knee osteoarthritis

The vastus medialis muscles are visualized as a white zone in the ultrasound image and imply enhanced muscle echo intensity (EI). As the white area within the muscle increases, the EI value increases, with a maximum of 255 (white).