Article

Journal of Orthopaedic Surgery

Journal of Orthopaedic Surgery
25(3) 1–11

DOI: 10.1177/2309499017743101
journals.sagepub.com/home/osj
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# Estimation of individual thigh muscle volumes from a single-slice muscle cross-sectional area and muscle thickness using magnetic resonance imaging in patients with knee osteoarthritis

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## Abstract

**Purpose:** This study aimed to identify the best single-slice anatomical muscle cross-sectional area (CSA) and muscle thickness (MT) on magnetic resonance imaging (MRI) to estimate the overall individual muscle volumes (MVs) of knee extensors and flexors in patients with knee osteoarthritis (KOA). **Methods:** Twelve patients (24 legs; 4 men and 8 women) with KOA underwent a 1.5-Tesla axial MRI scan in the femoral region of interest (ROI), between the lesser trochanter and rectus femoris tendon. Individual MVs were calculated by numerical integration based on individual CSAs analyzed at the ROI. The best slice was determined as follows: coefficient of determination ($R^2$) between MVs measured and those estimated from the femoral length (FL) $\times$ CSAs or FL $\times$ MTs measured at each 10% interval level of the ROI. These estimation equations were applied for a cross-validation group (24 KOA patients: 12 men and 12 women). **Results:** Estimated individual MVs of knee extensors and flexors, based on the CSAs at the distal 10% level, significantly correlated with each of the measured individual MVs ($R^2$: 0.79–0.96, $p < 0.05$ for all). Similarly, estimated individual knee extensor MVs, based on MTs at the mid-slice, significantly correlated with each of the measured individual MVs ($R^2$: 0.77–0.84, $p < 0.05$ for all). The application of the developed regression equation to the cross-validation group did not exhibit any systematic bias. **Conclusion:** These simple methods could be applied in prospective research with a larger number of patients with KOA.

## Keywords

individual muscle volumes, knee extensors, knee flexors, magnetic resonance imaging, simple estimation

Date received: 27 April 2017; Received revised 31 July 2017; accepted: 27 October 2017

## Introduction

Early diagnosis and prevention of frailty-related disorders, such as sarcopenia, with a high risk of falling are important in aging societies.[1,2] In particular, knee osteoarthritis (KOA) is a primary causative disease of frailty associated with a high risk of falling.[3] As knee deformity and painful knee due to KOA result in decreased muscle strength of the thigh, it is important to detect a risk factor for falls in the earlier stages of disease development. Measuring knee extension or flexion strength may be difficult because such measurements depend on the patient's ability to clearly

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understand the examinations or perform them without experiencing knee pain. Consequently, Blazevich et al.[4] proposed muscle volume (MV) measurement as a gold standard for estimating concentric muscle contraction during knee extension.

Regional or total body MVs have been measured using computed tomography, magnetic resonance imaging (MRI), and dual-energy X-ray absorptiometry and estimated using ultrasound.[5–12] Currently, some studies have reported that development and progression of KOA cannot be predicted using a single anatomical muscle cross-sectional area (CSA) when measuring knee extensors and flexors as a muscle group.[13–15] However, MRI provides greater detail and allows us to further divide a given muscle group into individual muscles because of its high-contrast resolution. Only a few studies used MRI to measure individual MVs of knee extensors in healthy subjects,[16–18] although there are few studies measuring individual MVs of knee extensors and flexors in KOA patients. Therefore, it remains unclear whether there are differences among individual muscles with regard to atrophy in the legs of KOA patients.

The analysis of individual knee extensors and flexors using serial images, sometimes over several dozens of images, is time-consuming. Therefore, a simple, precise methodology for individual MV estimation could enable clinical research in a larger number of patients. However, the level of CSA and muscle thickness (MT) that could accurately predict the overall individual MVs of extensors and flexors in KOA patients has not been determined. Tracy et al.[12] reported that the accuracy of estimation of the longitudinal change after hypertrophy in MV of knee extensors based on a single-slice CSA at the mid-thigh was markedly inferior compared with that from the estimation of MV at a time point prior to hypertrophy. Furthermore, in upper extremities, Roman et al.[19] reported that an increase in the ratio of CSA after resistance training was greater than that of MV. Measuring muscle changes based on a single-slice CSA could, therefore, result in an overestimation of the MV change. Similarly, muscle shape in healthy people may differ from that in KOA patients, primary and/or secondary to the pathologic atrophy of thigh muscles. Therefore, it is necessary to determine the specific level of CSA or MT for estimating MV in KOA patients.

This study aimed to demonstrate the best level of single-slice CSA and/or MT that would be useful for the quantification of individual knee extensor and flexor MVs in elderly patients without definitive KOA and in those with definitive KOA, and to validate them in a simple estimation of MVs from individual knee extensors and flexors.

## Materials and methods

### Patients

In this study, we included 36 patients (age 65–80 years) who complained of frequent pain ($\geq$3 months) in one and/or both knees at an outpatient examination, had received any care from physiotherapists, and were able to walk without using a cane. Based on the Kellgren–Lawrence classification using radiography, doubtful osteophytes and/or joint space narrowing were diagnosed as grade 1 and definitive osteophytes and joint space narrowing were diagnosed as grade $\geq$2.

A model development group included 12 patients (four men and eight women; both thighs): 13 legs had KOA grade 1 and 11 legs had KOA grade $\geq$2. Subject characteristics in the model development group were mean age, 73.7 $\pm$ 3.5 years; height, 154.7 $\pm$ 9.5 cm; weight, 63.5 $\pm$ 10.6 kg; and body mass index, 26.5 $\pm$ 2.5 kg/m$^2$. A cross-validation group included 24 patients (12 with KOA grade 1 and 12 with KOA grade $\geq$2; 6 men and 6 women in each group). The patients with KOA grade 1 who had a Japanese Knee Osteoarthritis Measure (JKOM) score of <30 points were recruited and regarded as elderly people who were almost healthy, whereas those with KOA grade $\geq$2 who had a JKOM score of $\geq$30 points were recruited and regarded as people with KOA-induced disuse. The side with the worse KOA grade was studied, and in patients with the same bilateral KOA grade, the painful side was studied. Subject characteristics in the cross-validation group were mean age, 74.3 $\pm$ 4.4 years; height, 155.2 $\pm$ 8.7 cm; weight, 64.6 $\pm$ 9.6 kg; and body mass index, 26.8 $\pm$ 3.3 kg/m$^2$. This study was conducted with the approval of the institutional review board. Informed consent was obtained from all individual participants included in the study.

### Femoral length analysis method

Femoral length (FL) was defined as the distance between the top of the greater trochanter and the intercondylar fossa of the femur, as measured from an anteroposterior femur radiograph by a trained image analyst using a digital image analysis system. The FL measurement, rather than the body height that was previously used by Sanada et al.,[7] was considered to be a more accurate predictor of the muscle length and was, thus, used to estimate individual MVs as FL $\times$ CSA or FL $\times$ MT.

### MRI acquisition

MRI of both legs was performed using a 1.5-T scanner (Excel ART; Toshiba Corp., Tokyo, Japan). Initially, a scout scan (repetition time/echo time (TR/TE), 185/15 ms; field of view, 400 mm; 128 $\times$ 256 matrix) of five 5-mm-thick coronal and sagittal slices at 5-mm intervals was performed to determine the coronal and sagittal femoral bone axis. Subjects were required to rest in the prone position with both legs lightly flexed for 15 min to avoid fluid shifts, and T1-weighted spin-echo with 10-mm-thick axial images (TR/TE, 625/15 ms; field of view, 250 mm; 512 $\times$ 512 matrix) were taken between the distal end of the lesser trochanter and the

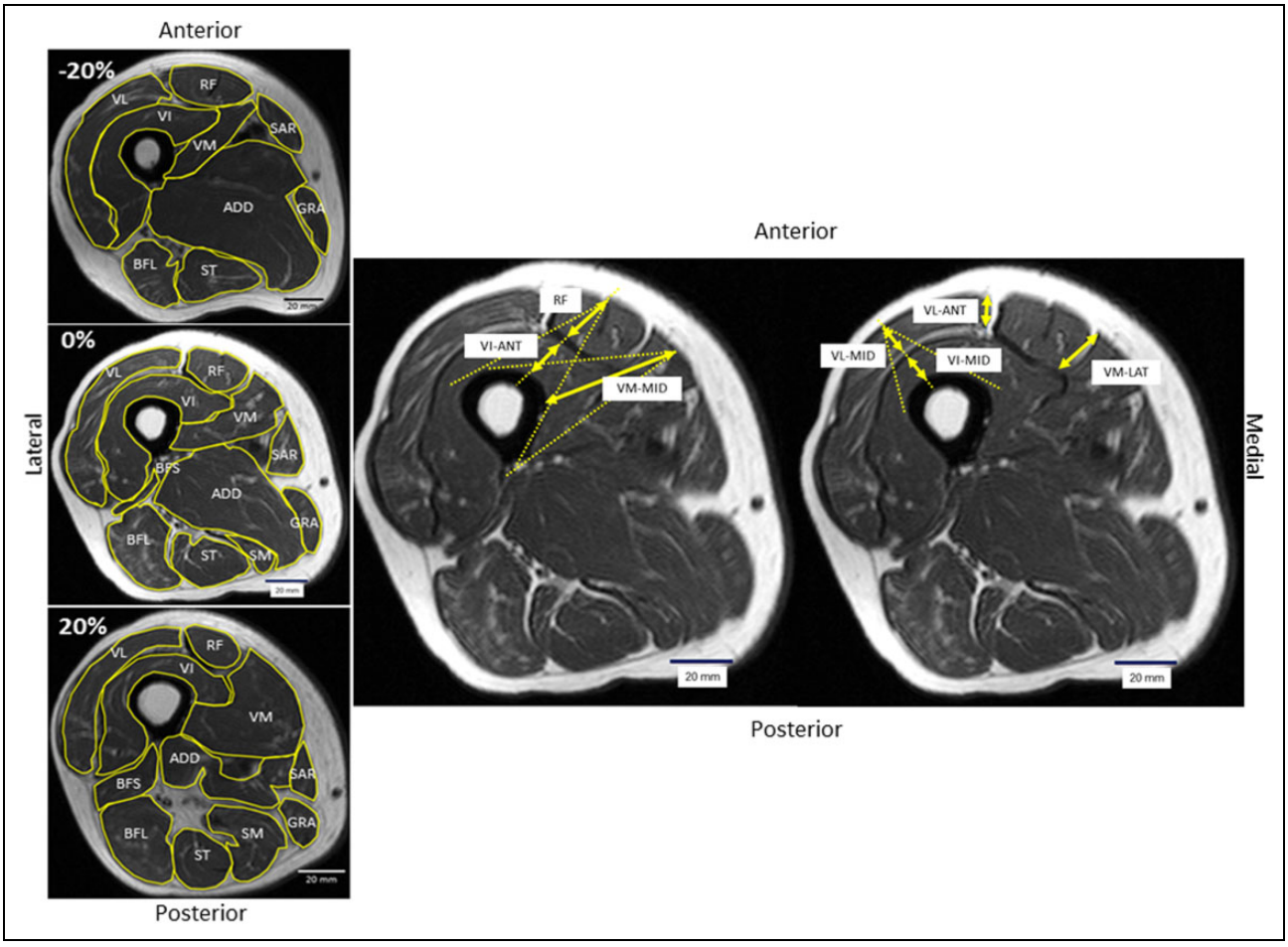


**Figure 1.** Typical example of segmented axial MR images of a right thigh at proximal 20%, 0% (mid-slice), and distal 20% levels of the femoral ROI. Segmented area shows the CSA of individual muscles (left figures). Right figures show a typical example of individual extensor MTs of the same thigh at the mid-slice. Two-way arrows show individual MTs of knee extensors. ANT: anterior; MID: middle; LAT: lateral; RF: rectus femoris; VL: vastus lateralis; VM: vastus medialis; VI: vastus intermedius; BFS: biceps femoris short head; BFL: biceps femoris long head; ST: semitendinosus; SM: semimembranosus; ADD: adductors; SAR: sartorius; GRA: gracilis; MT: muscle thickness; ROI: region of interest; CSA: cross-sectional area; MR: magnetic resonance.

proximal end of the patella with a 10-mm thickness. During scanning, patients' ankles were supported by a box to stabilize the neutral position and maintain the patellar direction to the right anterior.

### *CSA and MV analysis methods*

A region of interest (ROI) was determined between the distal end of the lesser trochanter and the proximal end of the rectus femoris (RF) tendon.[20] Consecutive CSAs corresponding to the ROI were measured by manually tracing the continuous axial images using Medical Image Processing, Analysis, and Visualization v7.3.0 software (National Institutes of Health, Bethesda, MD, USA; Figure 1). Visible intermuscular fat, vessels, and neuronal connective tissue were not included. To calculate the MV ($cm^3$) of total extensors, all CSA slices ($cm^2$) of RF, vastus lateralis (VL), vastus medialis (VM), and vastus intermedius (VI) were summed. To calculate the MV of total flexors, all CSA slices of biceps femoris short head (BFS), biceps femoris long head (BFL), semitendinosus (ST), and semimembranosus (SM) were summed. Muscle belly was defined as the maximum value of average CSA.

### *MT analysis method regarding RF, VL, VM, and VI*

We defined the MTs of RF, VL, VM, and VI from axial images as our original measurements (Figure 1). RF thickness was the distance from the superficial midpoint of the medial and lateral edge of RF to the cross-point of the middle line to the superficial bone. Two VL thicknesses were determined. Anterior thickness (VL-ANT) was the distance between the superficial medial edge and deep medial edge of VL. Middle thickness (VL-MID) was the distance from the superficial midpoint to the cross-point with the middle line to the superficial bone; the superficial midpoint was defined as the midpoint between the superficial medial edge and the right lateral point on the most

lateral bone surface. Two VI thicknesses were measured. VI-ANT was the distance under RF, and VI-MID was the distance under VL-MID. Two VM thicknesses were measured. Lateral thickness (VM-LAT) was the distance between superficial lateral edge and deep lateral edge of VM. VM-MID was the distance from the superficial midpoint of the medial and lateral edge of VM to the crosspoint with the middle line to the superficial bone. These MTs were measured at each 10% interval of the ROI. All measurements were performed by a trained image analyst.

### Statistics

To determine a predictable single slice for all individual MVs in the model development group, statistical analysis was conducted as follows. A correlation coefficient between the measured MV and the measured FL × CSA and FL × MT at each level was assessed using Spearman's correlation coefficient ($r_s$). An a priori power analysis showed that for a sample size of 12, $r = 0.72$ corresponded to a power of 0.8 and $p$ value of 0.05. Therefore, we defined the $r \geq 0.72$ with $p < 0.05$ as a strong correlation. The power analysis was performed in G*Power 3.1. (Heinrich Heine Universität, Düsseldorf, Germany).

Single slices that strongly correlated with all individual MVs were selected. Estimated MV was calculated using a single regression equation based on the measured FL × CSA or FL × MT. The absolute difference between the estimated and measured MVs (absolute residual) for individual MVs was compared to assess the accuracy of the estimation of MVs among the selected slices. Comparisons were undertaken using the nonparametric Friedman test with a post hoc test modified by the Bonferroni inequality. The coefficient of determination ($R^2$) was calculated using linear regression analysis to determine the degree of association between the estimated and measured MVs. The Bland–Altman analysis of each final regression equation was conducted to estimate individual MVs to check for systematic bias. The standard error of estimate (SEE (%)) was calculated from the sample size and the sum of the squared difference between the estimated and measured MVs divided by the measured MV.

All statistical tests were performed using SPSS statistical software (version 22; SPSS, Inc., Chicago, Illinois, USA). $P < 0.05$ was regarded as significant difference. All data are expressed as means and standard deviations.

## Results

### Where would a single-slice CSA best predict the average overall individual MVs of knee extensors and flexors?

CSA distributions in individual knee extensors and flexors measured at each of 10% interval of the ROI are shown in Figure 2. Correlations between FL × CSAs at each of 10% interval of the ROI and measured MVs of individual knee extensors and flexors are shown in Table 1. Generally, FL × CSAs at or near the muscle belly were strongly correlated with measured MVs ($r_s \geq 0.72$ with $p < 0.05$ for all). Moreover, FL × CSAs at the distal 10%, 20%, and 30% level were strongly correlated with all individual MVs ($r_s \geq 0.74$ with $p < 0.05$ for all). Comparisons of absolute residuals among the distal 10%, 20%, and 30% level were conducted (Table 2). The absolute residual based on the distal 30% level was significantly higher in ST ($p = 0.01$ for all). The absolute residual based on the distal 10% level was significantly lower than that of the distal 20% level in RF ($p < 0.01$) and VL ($p = 0.01$). On the other hand, in VM, the absolute residual based on the distal 10% level was significantly higher than that of the distal 20% level ($p = 0.01$). However, $R^2$ value at the distal 10% level of VM was high enough to estimate the MV ($R^2 = 0.91$). No significant differences were observed in other individual muscles. Therefore, the single slice at the distal 10% level was the best predictor of the average overall individual MVs.

A regression equation for estimating individual MVs ($cm^3$) from FL (cm) × CSAs ($cm^2$) at the distal 10% level is as follows: RF = FL × CSA × 0.56 + 17.9, VL = FL × CSA × 0.54 + 8.1, VM = FL × CSA × 0.44 + 32.3, VI = FL × CSA × 0.42 + 30.7, BFS = FL × CSA × 0.31 + 17.9, BFL = FL × CSA × 0.31 + 5.0, ST = FL × CSA × 0.41 + 18.2, and SM = FL × CSA × 0.34 + 20.8. Relationship between measured MVs and estimated MVs from FL and the distal 10% level CSAs was illustrated for the individual muscles of knee extensors and flexors (Figure 3).

### Where would a single-slice MT from each individual muscle best predict the average overall individual MVs of the extensors?

MT distributions in individual knee extensors at each of 10% interval of the ROI are shown in Figure 4. Correlations between FL × MTs at each of 10% interval of the ROI and measured MVs of individual extensor muscles are shown in Table 3. None of FL × VL-ANT MTs was significantly correlated with MV, whereas FL × MTs from the 0% (mid-slice) to distal 30% level were strongly correlated with all individual MVs ($r_s \geq 0.72$ with $p < 0.05$ for all).

Absolute residuals of the mid-slice, distal 10%, 20%, and 30% level MTs were compared (Table 4). No significant differences among the absolute residuals based on the mid-slice, distal 10%, 20%, and 30% level were observed in all individual muscles. Significant difference in the absolute residual based on the mid-slice between VI-ANT and VI-MID was observed ($p = 0.02$), while in the absolute residual based on the distal 10% level, VI-ANT had a tendency to be lower than VI-MID ($p = 0.05$). Thus, VI-ANT was a better predictor of VI MV than VI-MID. In addition, in RF and VM, mean absolute residuals at the mid-slice were the lowest and the $R^2$

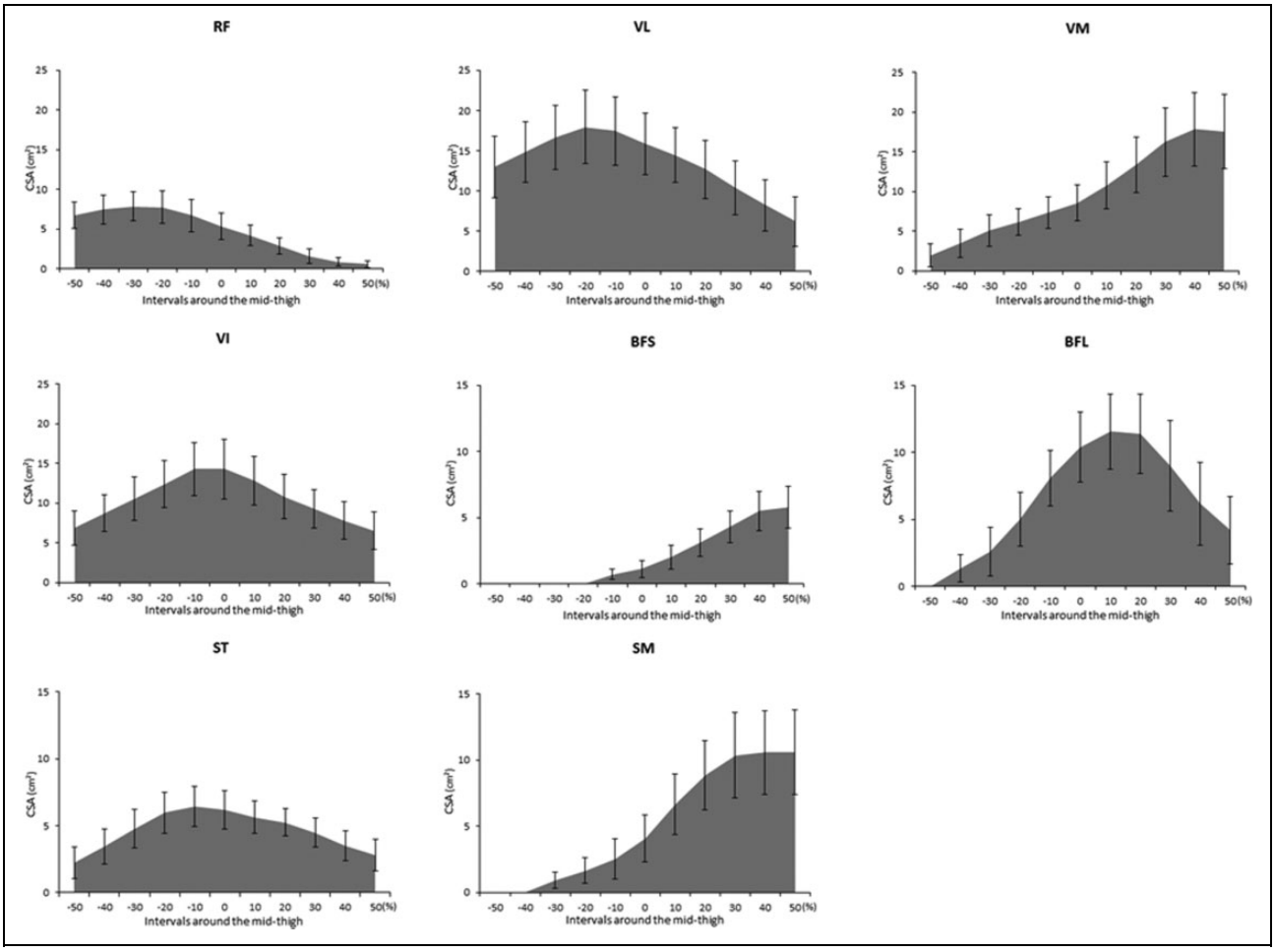


**Figure 2.** Distribution of individual extensor CSAs and individual flexor CSAs. Gray areas show distribution of mean CSAs at each 10% interval of the femoral ROI. Error bar means standard deviations. RF: rectus femoris; VL: vastus lateralis; VM: vastus medialis; VI: vastus intermedius; BFS: biceps femoris short head; BFL: biceps femoris long head; ST: semitendinosus; SM: semimembranosus; CSA: cross-sectional area; ROI: region of interest.

**Table 1.** Correlation between FL × CSAs at each level and individual MVs of knee extensors and flexors.[a]

| | | Location of thigh | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Proximal (%) | | | | | Mid | Distal (%) | | | | |
| | | −50 | −40 | −30 | −20 | −10 | 0 | 10 | 20 | 30 | 40 | 50 |
| Extensors | | | | | | | | | | | | |
| RF | $r_s$ | 0.86 | 0.88 | 0.94 | 0.95 | 0.96 | 0.97 | 0.98 | 0.90 | 0.90 | | |
| VL | $r_s$ | 0.81 | 0.88 | 0.92 | 0.95 | 0.95 | 0.95 | 0.92 | 0.89 | 0.93 | 0.88 | 0.86 |
| VM | $r_s$ | | | 0.83 | 0.88 | 0.86 | 0.92 | 0.94 | 0.94 | 0.95 | 0.94 | 0.91 |
| VI | $r_s$ | 0.77 | 0.74 | 0.83 | 0.92 | 0.94 | 0.94 | 0.95 | 0.95 | 0.89 | 0.80 | 0.87 |
| Flexors | | | | | | | | | | | | |
| BFS | $r_s$ | | | | | | | 0.74 | 0.91 | 0.97 | 0.92 | 0.86 |
| BFL | $r_s$ | | | | | 0.90 | 0.94 | 0.95 | 0.85 | 0.81 | 0.74 | 0.73 |
| ST | $r_s$ | | | 0.88 | 0.89 | 0.86 | 0.78 | 0.92 | 0.87 | 0.80 | | |
| SM | $r_s$ | | | | | | | 0.76 | 0.93 | 0.85 | 0.78 | 0.72 |

RF: rectus femoris; VL: vastus lateralis; VM: vastus medialis; VI: vastus intermedius; BFS: biceps femoris short head; BFL: biceps femoris long head; ST: semitendinosus; SM: semimembranosus; MV: muscle volume; FL: femoral length; CSA: cross-sectional area.
[a]Values show a correlation coefficient $\geq 0.72$ with $p < 0.05$. $r_s$ means Spearman's correlation coefficient.

**Table 2.** Comparison of the degree of accuracy and association in terms of regression equations based on FL × CSAs.[a]

| | $R^2$ | | | Absolute residual ($cm^3$) | | | |
|---|---|---|---|---|---|---|---|
| | +10% | +20% | +30% | +10% | +20% | +30% | *p* Values |
| Extensors | | | | | | | |
| RF | 0.96 | 0.87 | 0.75 | 5.5 ± 4.8[b,c] | 11.1 ± 6.9[b] | 15.2 ± 9.7[c] | <0.01 |
| VL | 0.95 | 0.90 | 0.92 | 15.6 ± 12.5[b] | 23.4 ± 18.2[b] | 21.2 ± 16.9 | 0.04 |
| VM | 0.91 | 0.96 | 0.96 | 15.2 ± 11.9[b,c] | 9.7 ± 8.6[b] | 9.3 ± 8.3[c] | 0.02 |
| VI | 0.92 | 0.95 | 0.91 | 15.7 ± 13.5 | 13.2 ± 9.0 | 17.4 ± 12.4 | 0.28 |
| Flexors | | | | | | | |
| BFS | 0.79 | 0.88 | 0.92 | 4.5 ± 3.2 | 2.9 ± 3.0 | 2.6 ± 2.2 | 0.07 |
| BFL | 0.93 | 0.86 | 0.77 | 10.0 ± 7.8 | 13.0 ± 12.3 | 18.1 ± 13.7 | 0.08 |
| ST | 0.87 | 0.71 | 0.57 | 8.3 ± 4.5[b] | 11.5 ± 8.1[c] | 14.3 ± 9.7[b,c] | 0.04 |
| SM | 0.85 | 0.89 | 0.81 | 10.9 ± 8.5 | 9.6 ± 7.0 | 12.3 ± 9.6 | 0.58 |

RF: rectus femoris; VL: vastus lateralis; VM: vastus medialis; VI: vastus intermedius; BFS: biceps femoris short head; BFL: biceps femoris long head; ST: semitendinosus; SM: semimembranosus; FL: femoral length; CSA: cross-sectional area.
[a]$R^2$ means coefficient of determination between estimated muscle volumes (MVs) and measured MVs ($p < 0.05$ for all). Absolute residual means the absolute difference between the estimated and measured MVs. Values show mean ± standard deviation.
[b,c]Same alphabets in one muscle mean significant difference ($p < 0.016$).

values were the highest. In VM, the mean absolute residual of VM-MID was lower than that of VM-LAT. Therefore, RF, VL-MID, VM-MID, and VI-ANT at the mid-slice may be the best predictor of individual MVs.

A regression equation for estimating individual MVs ($cm^3$) from FL (cm) × MTs (cm) at the mid-slice is as follows: RF = FL × MT × 1.6 + 24.7, VL = FL × MT × 3.9 + 83.9, VM = FL × MT × 1.8 − 30.4, VI = FL × MT × 3.8 + 75.5. Relationship between measured MVs and estimated MVs from FL and the mid-slice MTs was illustrated for the individual muscles of knee extensors (Figure 5).

The Bland-Altman analysis of each final regression equation estimated individual MVs of knee extensors and flexors in the model development group was conducted. No significant differences were observed between the measured and estimated MVs in any of the studied individual muscles. Furthermore, no significant correlations were observed between the difference and mean value of the measured and estimated individual MVs in the Bland–Altman plots. In terms of estimation based on FL and CSA at the distal 10% level, SEE was 6.6% for RF, 6.3% for VL, 8.6% for VM, 8.1% for VI (5.1% for knee extensor), 16.5% for BFS, 9.1% for BFL, 8.6% for ST, and 14.2% for SM (6.5% for knee flexor). In terms of the estimation based on FL and MT at the mid-slice level, SEE was 15.3% for RF, 13.0% for VL, 10.6% for VM, and 11.2% for VI (6.7% for knee extensor).

## *Bland–Altman analysis for cross validation of the final regression equations*

Regression equations based on the model development group were applied for estimating MVs in the cross-validation group. No significant differences between measured and estimated MVs were observed in individual muscles. No significant correlations were observed between the difference and mean value of measured and estimated individual MVs in the Bland–Altman plots. However, estimation based on BFS CSA, ST CSA, and RF MT showed a positive correlation tendency between the difference (measured MV − estimated MV) and mean value of the measured and estimated MVs ($r = 0.39$ with $p = 0.06$ for BFS CSA, $r = 0.39$ with $p = 0.06$ for ST CSA, and $r = 0.40$ with $p = 0.05$ for RF MT).

With regard to the estimation based on FL and CSA at the distal 10% level, SEE was 12.5% for RF, 7.1% for VL, 8.1% for VM, 7.5% for VI (5.3% for knee extensor), 14.4% for BFS, 7.2% for BFL, 10.9% for ST, and 13.9% for SM (4.8% for knee flexor). In terms of estimation based on FL and MT at the mid-slice level, SEE was 21.8% for RF, 13.0% for VL, 18.6% for VM, and 15.5% for VI (12.4% for knee extensor).

In the cross-validation group, no significant differences were observed in the absolute difference between measured and estimated MVs of patients with KOA grades 1 and ≥2 in any of the studied individual muscles. The SEEs based on FL and CSA at the distal 10% level of patients with KOA grades 1 and ≥2 were 11.8% and 13.2% for RF, 7.1% and 7.1% for VL, 6.7% and 9.3% for VM, 8.4% and 6.5% for VI (5.6% and 5.1% for knee extensor), 18.0% and 9.7% for BFS, 7.2% and 7.2% for BFL, 12.5% and 8.9% for ST, and 11.3% and 16.1% for SM (5.0% and 4.7% for knee flexor). However, the SEEs based on FL and MT at the mid-slice level of patients with KOA grades 1 and ≥2 were 16.0% and 20.8% for RF, 10.8% and 10.3% for VL, 12.6% and 19.4% for VM, and 10.7% and 16.0% for VI (9.8% and 10.7% for knee extensor), respectively.

## *Reproducibility for the test–retest of CSA and MT measurement in the individual muscles of knee extensors and flexors*

In our pilot study, MRI scans of the right thigh of the five subjects were performed two times with repositioning of

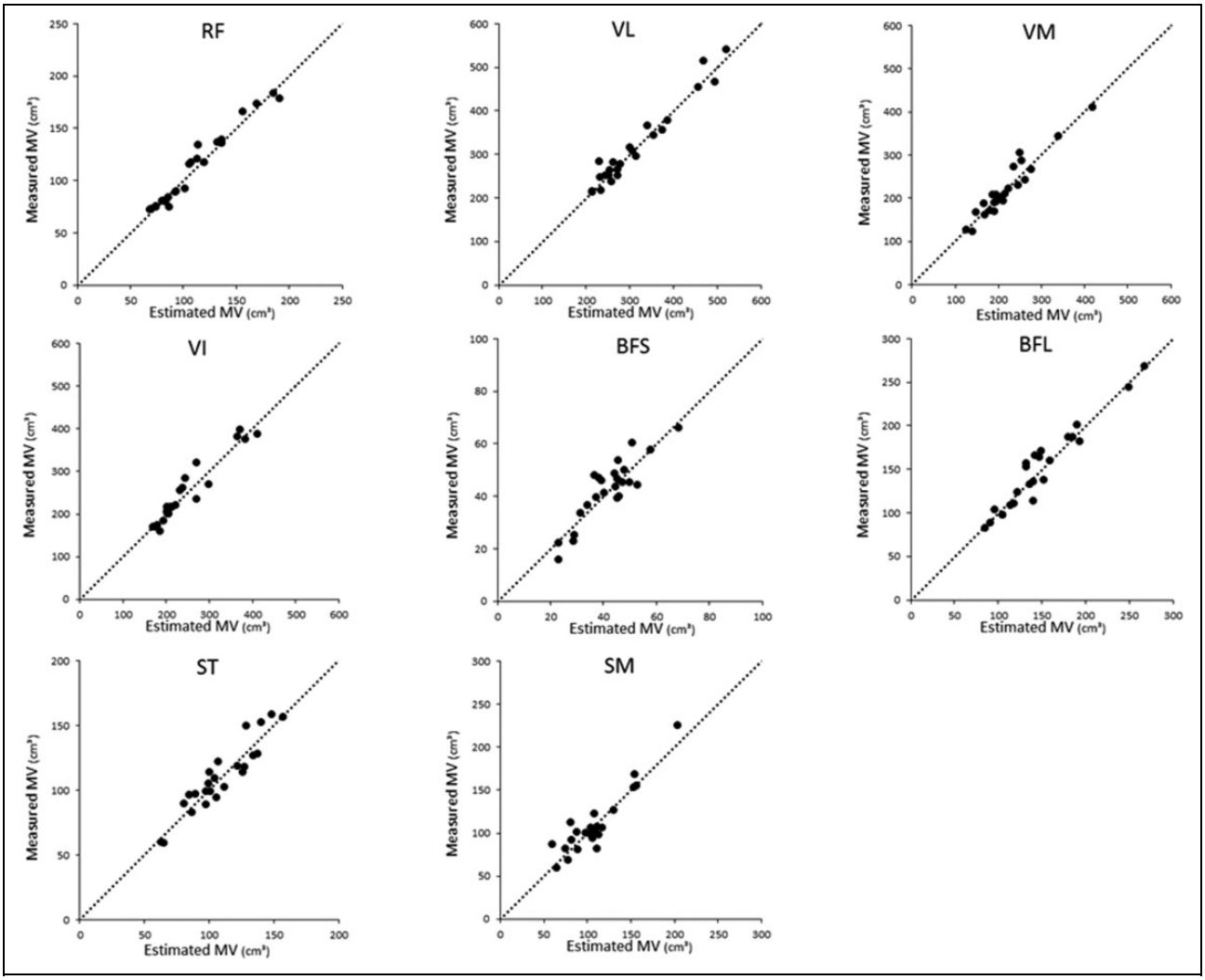


**Figure 3.** Relationship between measured MVs and estimated MVs from FL and CSAs at the distal 10% level. $R^2$ value was 0.96 for RF, 0.95 for VL, 0.91 for VM, 0.92 for VI, 0.79 for BFS, 0.93 for BFL, 0.87 for ST, and 0.85 for SM, all *p*s < 0.05. Dotted lines represent the identity line. RF: rectus femoris; VL: vastus lateralis; VM: vastus medialis; VI: vastus intermedius; BFS: biceps femoris short head; BFL: biceps femoris long head; ST: semitendinosus; SM: semimembranosus; MV: muscle volume; FL: femoral length; CSA: cross-sectional area.

the subjects after the first scan. The trained image analyst measured individual CSAs and MTs of each three slices scanned around the mid-slice of the ROI. Intraclass correlation coefficient (ICC) and the root mean square (CV%) were calculated. In terms of the test–retest reproducibility of individual CSA measurement of knee extensors and flexors, ICC (95% confidence interval (CI)) ranged from 0.97 (0.90–0.99) for BFS to 1.00 (0.98–1.00) for RF, while CV% ranged from 8.5% for BFS to 1.7% for RF. In terms of the reproducibility of individual MT measurement of knee extensors, ICC (95% CI) ranged from 0.95 (0.84–0.98) for VL-MID to 0.99 (0.97–1.00) for RF, while CV% ranged from 4.2% for VL-MID to 3.1% for RF. Thus, the reproducibility of CSA and MT measurement was excellent in this study. However, in terms of individual knee flexors, we were unable to define the deep points of each individual flexor, which suggested poor reproducibility to estimate the individual flexors' MVs from the MTs. Therefore, this study did not include the individual flexor MTs.

## Discussion

Previous studies aimed to estimate the total MVs of extensors and/or flexors using the CSA or MT.[7,10,11,17] In contrast, no published studies estimated the individual MVs of extensors and flexors using a single-slice CSA or estimated the individual MVs of extensors using MTs. The novel finding of the present study is that the single-slice CSA at the distal 10% level from the mid-slice yielded the best predictions of individual extensor and flexor MVs.

Some authors observed strongest correlation between CSA and MV at or near the muscle belly in healthy people.[8,17] In our study, we found that the $R^2$ value to estimate MVs based on the muscle belly CSA was 0.96 for RF, 0.96

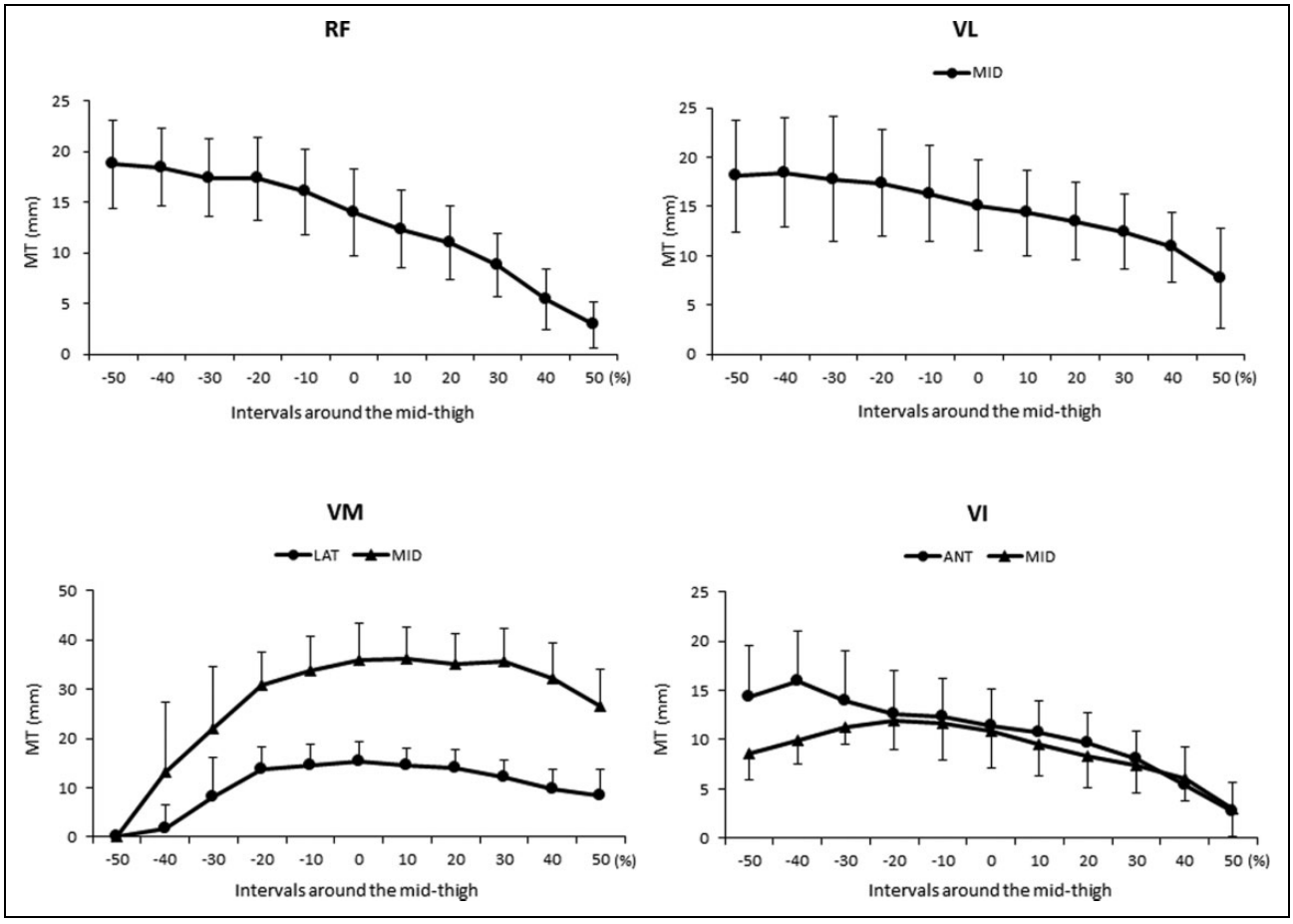


**Figure 4.** Distribution of individual extensor MTs. Line graphs show distribution of mean MT of RF, VL-MID, VM-LAT, VM-MID, VI-ANT, and VI-MID. Error bar means standard deviations. RF: rectus femoris; VL: vastus lateralis; VM: vastus medialis; VI: vastus intermedius; ANT: anterior; MID: middle; LAT: lateral; MT: muscle thickness.

**Table 3.** Correlation between FL × MTs at each level and individual MVs of knee extensors.[a]

| | | Location of thigh | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Proximal (%) | | | | | Mid | Distal (%) | | | | |
| Muscle thickness | | −50 | −40 | −30 | −20 | −10 | 0 | 10 | 20 | 30 | 40 | 50 |
| RF | $r_s$ | 0.83 | 0.88 | 0.84 | 0.83 | 0.84 | 0.87 | 0.76 | 0.78 | 0.78 | | |
| VL-ANT | $r_s$ | | | | | | | | | | | |
| VL-MID | $r_s$ | | | 0.80 | | | 0.73 | 0.80 | 0.72 | 0.74 | 0.82 | |
| VM-LAT | $r_s$ | | | | | 0.81 | 0.82 | 0.77 | 0.81 | 0.87 | 0.84 | |
| VM-MID | $r_s$ | | | | 0.85 | 0.90 | 0.96 | 0.96 | 0.90 | 0.94 | 0.95 | |
| VI-ANT | $r_s$ | | | 0.72 | 0.76 | 0.72 | 0.90 | 0.93 | 0.84 | 0.86 | 0.72 | |
| VI-MID | $r_s$ | | | 0.77 | 0.83 | 0.77 | 0.76 | 0.86 | 0.81 | 0.84 | 0.86 | |

RF: rectus femoris; VL: vastus lateralis; VM: vastus medialis; VI: vastus intermedius; ANT: anterior; MID: middle; LAT: lateral; FL: femoral length; MV: muscle volume; MT: muscle thickness.

[a]Values show a correlation coefficient $\geq 0.72$ with $p < 0.05$. $r_s$ means Spearman's correlation coefficient.

for VL, 0.89 for VM, and 0.92 for VI in individual knee extensors, and 0.60 for BFS, 0.93 for BFL, 0.85 for ST, and 0.71 for SM in individual knee flexors (data not shown). These $R^2$ values based on the muscle belly CSAs were similar to or relatively lower than those based on the distal 10% CSAs. Akima et al.[21] reported that muscle atrophy in knee extensors and flexors due to bed rest was observed to be maximal around the muscle belly and that both ends of these muscles did not change significantly. Therefore, in patients with muscle atrophy, MV estimation based on the

**Table 4.** Comparison of the degree of accuracy and association in terms of regression equations based on FL × MTs.[a]

| | $R^2$ | | | | Absolute residual ($cm^3$) | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 0% | +10% | +20% | +30% | 0% | +10% | +20% | +30% | *p* Values |
| RF | 0.77 | 0.61 | 0.65 | 0.69 | 14.6 ± 9.3 | 19.1 ± 12.4 | 17.7 ± 12.3 | 16.3 ± 11.8 | 0.27 |
| VL-MID | 0.84 | 0.84 | 0.80 | 0.75 | 32.9 ± 18.3 | 29.7 ± 22.7 | 35.7 ± 20.5 | 37.4 ± 27.4 | 0.59 |
| VM-LAT | 0.83 | 0.76 | 0.76 | 0.73 | 22.8 ± 15.5 | 26.1 ± 19.6 | 26.9 ± 18.2 | 27.4 ± 21.0 | 0.49 |
| VM-MID | 0.82 | 0.76 | 0.78 | 0.78 | 20.7 ± 19.0 | 23.8 ± 22.2 | 25.3 ± 17.7 | 22.2 ± 22.1 | 0.62 |
| VI-ANT | 0.81 | 0.86 | 0.79 | 0.83 | 22.7 ± 22.1[b] | 19.4 ± 18.9[c] | 25.7 ± 20.8 | 23.3 ± 19.6 | 0.31 |
| VI-MID | 0.63 | 0.65 | 0.71 | 0.77 | 34.3 ± 28.4[b] | 31.4 ± 29.8[c] | 29.9 ± 25.6 | 28.2 ± 21.3 | 0.38 |

RF: rectus femoris; VL: vastus lateralis; VM: vastus medialis; VI: vastus intermedius; ANT: anterior; MID: middle; LAT: lateral; FL: femoral length; MT: muscle thickness.

[a]$R^2$ means coefficient of determination between estimated muscle volumes (MVs) and measured MVs ($p < 0.05$ for all). Absolute residual means the absolute difference between the estimated and measured MVs. Values show mean ± standard deviation.

[b]Significant difference between VI-ANT and VI-MID at the 0% slice ($p = 0.02$).

[c]A tendency to be difference between VI-ANT and VI-MID at the +10% level with $p = 0.05$.

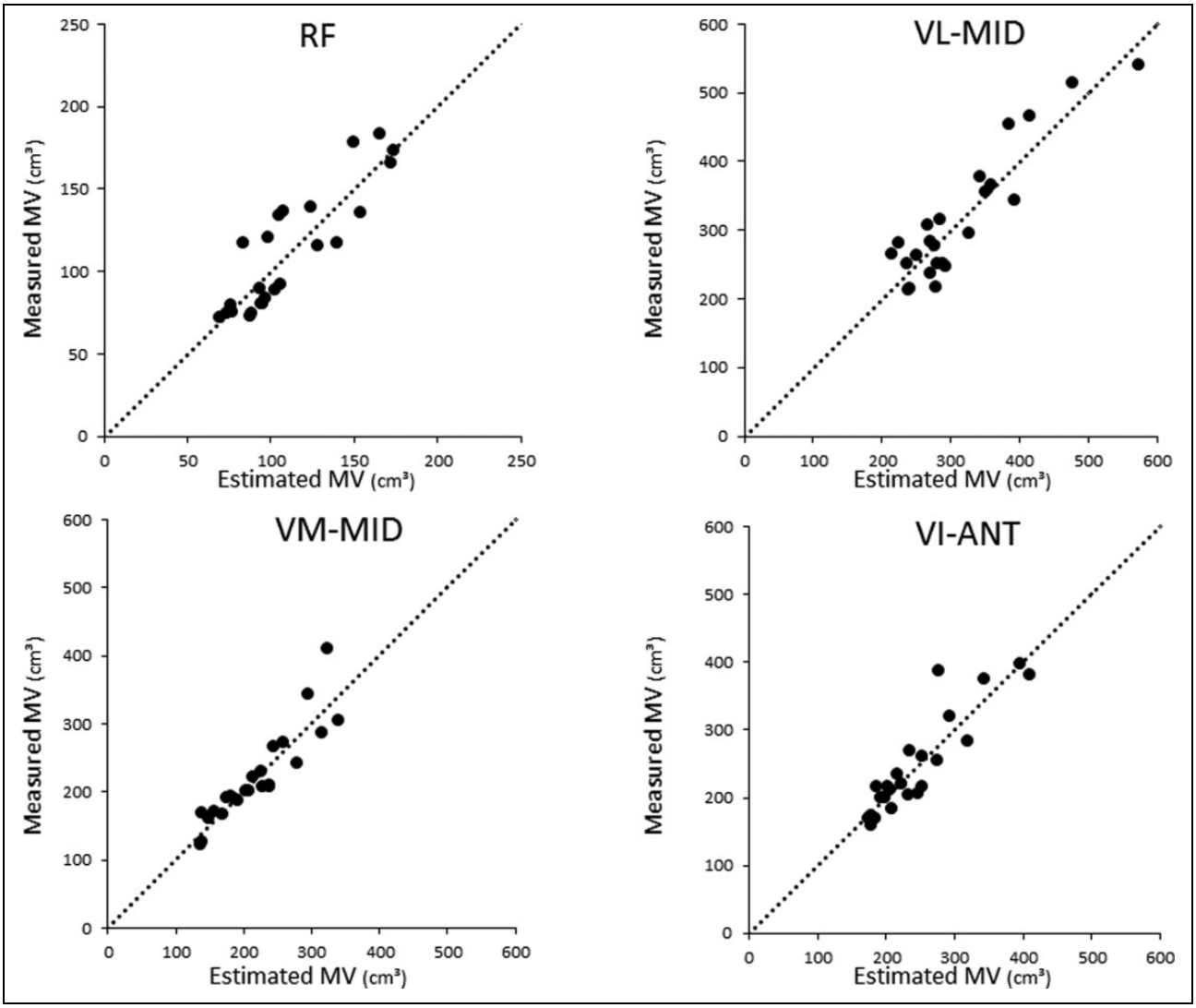


**Figure 5.** Relationship between measured MVs and estimated MVs from FL and MTs at the 0% level. $R^2$ value was 0.77 for RF, 0.84 for VL-MID, 0.82 for VM-MID, and 0.81 for VI-ANT, all *p*s < 0.05. Dotted lines represent the identity line. RF: rectus femoris; VL: vastus lateralis; VM: vastus medialis; VI: vastus intermedius; ANT: anterior; MID: middle; MV: muscle volume; FL: femoral length; MT: muscle thickness.

muscle belly CSAs leads to an overestimation, whereas MV estimation based on muscle end CSAs leads to an underestimation. The relationship between the muscle belly CSA and MV, observed in healthy people, may be affected by KOA; that is, we suppose that individual muscle shapes in KOA patients differ from those in healthy people. This study demonstrated that although the magnitude of individual MV changes may vary according to disease-related variabilities in the KOA grade, individual MVs could be estimated from a single-slice CSA at the distal 10% level. The distal 10% level was around the center between the muscle belly and muscle end in individual muscles except BFL. In contrast, the SEE from MTs at the mid-slice level had a greater value in patients with progressive KOA (grade $\geq$2) but the difference was not significant. The accuracy of the estimate using MT measurement may be affected by muscle atrophy more strongly than the CSA measurement.

In addition, the single-slice CSA at the distal 10% level reflected the total MVs of extensors and flexors more accurately than that reported in other studies. Tracy et al.[12] reported an SEE of 7.1% when estimating knee extensor MV in healthy people based on the maximum CSA level (muscle belly). Morse et al.[17] reported that the SEE was 9.9% when estimating knee extensor MV in healthy young people based on the CSA corresponding to the distal 20% level in the present study. Although some authors have proposed that single anatomical muscle CSA measurement in knee extensor and flexor could not predict the development and progression of KOA, their measured CSA corresponded to the distal 30–50% level in this study, which might be too distal a level to accurately reflect MVs.[13–15] In future research, more studies may be needed to demonstrate which methods of MV, CSA, or MT measurements may be most useful to sensitively detect disease-related muscle change in early stage KOA.

In terms of the individual extensor MTs, there was a site-specific variation between the correlation coefficients of MT and MV even within the same muscle (e.g. ANT, MID, and LAT in the same muscle). MT measurement defined in the present study can be measured using an ultrasound device. The use of an ultrasound device to estimate individual knee extensor MVs will be more beneficial in clinics with regard to both time and cost consumption than that of MRI. To increase the reproducibility of MT measurement using an ultrasound device, it was important to determine the definitive two points for the measurement of each MT, the superficial and deep points. In addition, the superficial and deep points that were clearly distinguished by an ultrasound device should be selected. The superficial points were determined using the superficial edges of individual muscles, whereas deep points were determined using the width of the femoral bone surface. However, with regard to the accuracy of individual MV estimates, the SEE based on MT measurement was higher than that based on CSA measurement. More studies are required to assess the reproducibility and validity of MT measurements in the individual muscles using ultrasound devices.

In conclusion, individual MVs of knee extensors and flexors of patients with KOA can be estimated from a single-slice CSA using MRI. Further, MVs of individual extensors may be estimated from the MT of a single slice. These simple methods used in this study should be applied in cross-sectional prospective research with a larger number of patients with KOA to ascertain differences among individual MVs of extensors and flexors.

## Author's note

This study was performed at Akita Hospital.

## Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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