Association between Sarcopenia/Lower Muscle Mass and Short-Term Regression of Deep Vein Thrombosis Using Direct Oral Anticoagulants

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Summary

Advanced age, obesity, and muscle weakness are independent factors in the onset of deep vein thrombosis (DVT). Recently, an association between sarcopenia and DVT has been reported. We hypothesized that sarcopenia-related factors, observed by ultrasonography, are associated with the regression effect on the thrombus following anticoagulation therapy. The present study focused on gastrocnemius muscle (GCM) thickness and the GCM’s internal echogenic brightness. We examined the association with DVT regression following direct oral anticoagulants (DOACs) treatment.

The prospective cohort study period was between October 2017 and August 2018. We enrolled 46 patients diagnosed with DVT by ultrasonography, who were aged >60 years old and treated with DOACs. Sarcopenia was evaluated using the Asian Working Group for Sarcopenia flowchart. The average DOACs treatment period was 94 days, and 29 patients exhibited thrombus regression. On univariate logistic regression analysis, sarcopenia, average GCM diameter index, and gastrocnemius integrated backscatter index were significantly associated with thrombus regression. In a multivariate model, only the average GCM diameter index correlated with thrombus regression.

The average GCM diameter index is associated with DVT regression treated with DOACs. Considering the GCM diameter during DVT treatment can be a marker to make a decision for the treatment of DVT.

Key words: Prediction, Anticoagulation, Integrated backscatter, Duplex ultrasound

The early detection and treatment of deep vein thrombosis (DVT), a major cause of pulmonary thromboembolism, is important in clinical practice. The number of patients with venous thromboembolism (VTE) is increasing steadily1,2 and indications for direct acting oral anticoagulants (DOACs) have expanded. Long-term anticoagulant treatment is highly effective in preventing recurrent VTE. However, the optimal duration for this therapy remains uncertain.3,4 One possible reason is that DVT recurrence or regression factors have not been well validated, although its pathogenic factors are well known.

Sarcopenia, one cause of DVT development,3,5 is defined as an age-related decrease in muscle mass and performance.6 Progressive decline in muscle mass, occurring between the ages of 40 and 80 years, is estimated at 30-50%,7,8 with associated reductions in functional capacity. It is a significant clinical problem for elderly individuals, causing decreased venous pump function with consequent ambulatory venous hypertension. Elderly patients are, therefore, more likely to develop DVT than young or active individuals. Because of these physiological mechanisms, sarcopenia related factors (e.g., muscle mass and performance) may be associated with DVT regression.

Ultrasonography can assess muscle echogenic brightness related to intramuscular fat mass and muscle thickness accurately.9,10 Thus, we hypothesized that sarcopenia related factors, assessed by ultrasonography, are associated with the regression effect on the thrombus following anticoagulation therapy. This study aimed to examine the as-
association between the regression effect on DVT following DOACs treatment and ultrasonographic parameters. We focused on gastrocnemius muscle (GCM) thickness and its internal echogenic brightness.

**Methods**

**Study population:** A single-center, prospective study was designed, and 65 DVT patients treated with DOACs over 60 years old (from the diagnostic criteria for Asian Working Group for Sarcopenia (AWGS group) flowchart described below) were initially enrolled. The Institutional Review Board of the Tokushima University Hospital approved the study protocol. The study covered the period between October 2017 and August 2018. Exclusion criteria were as follows: patients with changes in DOAC prescription \((n = 7)\), incomplete sonographic data \((n = 9)\), and dropout \((n = 3)\). Following exclusion, 46 patients diagnosed with DVT remained for final analysis, who were treated with DOACs following diagnosis with DVT by ultrasonography (Figure 1). The DOAC doses for all patients was determined by the attending physician, taking the risk of bleeding into account. The DOACs high dose group was defined as patients who were initially treated with apixaban 20 mg/day, edoxaban 60 mg/day, or rivaroxaban 30 mg/day. On the other hand, the DOACs low dose group was defined as patients who started treatment with apixaban 10 mg/day, edoxaban 30 mg/day, or rivaroxaban 15 mg/day.

**Standard ultrasonography:** Ultrasonography was performed using a commercially available ultrasound machine (Logiq 7; GE Healthcare, Waukesha, WI). In all tests, a whole leg scan was performed, and the presence or absence of DVT was evaluated by the compression method. At the same time, muscle thickness and internal echogenic brightness of the GCM were evaluated. The patient was placed in the supine position, and the leg was scanned,\(^{13}\) the entire GCM was scanned, and the maximum straight-line distance of the surface fascia and deep fascia of the GCM was measured in a transverse scan, which was taken as the GCM thickness. The ultrasound measurement screen was set at 5 cm depth, 2 cm focus, and unified in all patients. In all cases, the integrated backscatter (IB) value was measured at a depth of 2 cm from the body surface. Severe subcutaneous edema affecting the IB measurement value was not included. Figure 2 shows representative cases with DOACs treatment.

**Evaluation of DVT regression:** Compression ultrasonography of the affected leg was performed, and images were obtained in transverse section only. Lumen compressibility was then evaluated by gently applying pressure with the probe. The residual venous thrombosis diameter was determined by measuring the distance between the anterior and posterior walls of the vein, on freeze-frame B-mode images, during compression with the ultrasound probe.\(^{13,14}\) The examination was performed with the patient in the supine position, with the leg externally rotated and slightly flexed at the knee. The maximum DVT diameter was used during whole leg scans. Also, if there were multiple DVTs, the maximum diameter of the central DVT was used in the analysis. DVT regression was calculated as follows: \(DVT = \frac{\left(\text{DVT diameter before treatment} - \text{DVT diameter after treatment}\right) \times 100}{\text{DVT diameter before treatment}}\). The primary endpoint was DVT regression defined when the figure was \(\leq 40\%\) of the vein diameter after treatment of DOACs.\(^{15}\)

**Diagnosis of sarcopenia:** A multi-frequency bioelectrical impedance analyzer, the Inbody S10 Biospace device (Inbody S10; Inbody, Tokyo, Japan), was used according to the manufacturer’s guidelines. Bioelectrical impedance analysis estimates body composition by using differences in conductivity of various tissues, caused by their different biological characteristics. In practice, the electrodes were placed at eight precise tactile-points of the body to achieve a multi-segment frequency analysis. The skeletal muscle mass index (SMI) was calculated by dividing the appendicular lean mass by height squared. Supplemental Figure 1 shows the evaluation of sarcopenia using the

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**Figure 1.** Flow chart of the recruitment of patients. DOACs indicates direct oral anticoagulants; and DVT, deep vein thrombosis.
Statistical analysis: Continuous data are expressed as the mean ± standard deviation. Categorical data are presented as absolute numbers and percentages. We compared the baseline characteristics between the two groups using analysis of variance or two tests, as appropriate. Continuous variables were compared using an unpaired Student’s t-test or Mann-Whitney U test, whereas categorical variables were compared using the chi-square test or Fisher’s exact test. Logistic regression analysis was used to evaluate the associations between several potential variables and DVT regression. Identified variables (P < 0.20 in the univariate model) were entered, in a stepwise manner, into a multivariate regression model. Age was assessed in the final model since they were suspected to influence DVT regression. The DeLong method was used to compare the C statistic. Reproducibility is expressed as the mean percentage error (absolute difference divided by the average of the two observations). One observer performed measurements on all patients; then two observers repeated measurements on two separate days. The latter two observers were unaware of the other’s measurements or study time point. The intra- and interobserver variabilities of the Ave. GCM diameter index were 3.0 ± 2.3% and 3.1 ± 2.6%, respectively. The Ave. GCM IB index values were 4.5 ± 2.2% and 4.1 ± 2.4%, respectively. Supplemental Figure 2 shows the Bland-Altman plots to assess interobserver variability, since the IB value is a new method. All statistical analyses were performed with SPSS 25.0 (IBM Corp., Armonk, NY, USA) and MedCalc 15.8 (Mariakerke, Belgium). P < 0.05 was considered statistically significant.

Results

Patient characteristics: Table I shows clinical and ultrasoundographic variables. A total of 46 DVT patients (mean age 72 ± 11 years; 37% male) were enrolled. DVT reduced in 96% of all patients after DOAC treatment. Over a period of 94 ± 23 days, 29 (63%) patients exhibited a significant regression in DVT. In DVT regression group, DVT diameter decreased from 4.0 mm to 1.3 mm after treatment (70% regression, P < 0.001). In DVT non-regression group, DVT diameter showed minimal change from 4.4 mm to 3.8 mm (13% regression, P = 0.25) (Figure 3). No significant differences were observed with regard to age, gender, body mass index, and symptoms between the DVT regression group and the DVT non-regression group. The DVT regression group had less sarcopenia (10 versus 35%, P = 0.02), larger Ave. GCM diameter index (10.2 ± 1.6 versus 7.9 ± 1.1 mm/m², P < 0.001) and lower Ave. GCM IB index (~67.4 ± 3.5 versus ~62.1 ± 4.3 dB, P < 0.001) compared with DVT non-regression group. There were no significant differences in treatment period, DOACs dosage, DOACs types and presence of active cancer between the two groups. Furthermore, Inbody parameters showed no significant differences between the two groups.

Prediction of DVT regression: To determine the factors associated with DVT regression, univariate and multivariate logistic regression analyses were performed to associate patient characteristics and sonographic variables with DVT regression. In the univariate model, DVT regression was correlated with sarcopenia, Ave. GCM diameter index and Ave. GCM IB index. In the multivariate models, DVT regression was correlated with Ave. GCM diameter index (OR = 4.104, P = 0.001) and GCM IB index (OR = 1.485, P = 0.002) after adjustment for age (Table II).

Figure 4 shows the results of the Receiver Operating Characteristic (ROC) analysis used to identify the optimal cut-off point for predicting DVT regression. ROC analyses
Table 1. Clinical and Ultrasonographic Variables

| Variable | All (n = 46) | DVT regression group (n = 29) | DVT non-regression group (n = 17) | P value |
|----------|-------------|-----------------------------|----------------------------------|--------|
| Age (years) | 72 ± 11 | 72 ± 13 | 72 ± 9 | 0.46 |
| Male (n, %) | 17 (37%) | 12 (41%) | 5 (29%) | 0.21 |
| Body surface area (m²) | 1.59 ± 0.23 | 1.62 ± 0.24 | 1.53 ± 0.21 | 0.09 |
| Body mass index (kg/m²) | 24.0 ± 4.8 | 24.3 ± 5.0 | 23.5 ± 4.2 | 0.28 |
| Handgrip strength (kg) | 21.6 ± 8.7 | 22.7 ± 9.3 | 19.8 ± 7.0 | 0.14 |
| Sarcopenia (n, %) | 9 (20%) | 3 (10%) | 6 (35%) | 0.02 |
| Symptom (n, %) | 25 (54%) | 17 (59%) | 8 (47%) | 0.23 |
| Active cancer (n, %) | 14 (30%) | 8 (28%) | 6 (35%) | 0.30 |
| Ave. lower leg measurement (mm) | 34.0 ± 4.9 | 34.7 ± 5.1 | 32.9 ± 4.1 | 0.12 |
| eGFR (mL/minute/1.73 m²) | 68 ± 16 | 66 ± 15 | 72 ± 18 | 0.11 |
| D-dimer (μg/mL) | 13.6 ± 7.3 | 14.6 ± 7.5 | 11.9 ± 7.1 | 0.31 |
| ΔD-dimer (μg/mL) | 10.4 ± 3.3 | 10.8 ± 2.8 | 9.8 ± 3.5 | 0.43 |
| Treatment period (days) | 94 ± 23 | 95 ± 25 | 91 ± 20 | 0.29 |
| DOACs high dose | 20 (43%) | 13 (65%) | 7 (35%) | 0.41 |
| DOACs low dose | 26 (57%) | 16 (62%) | 10 (38%) | 0.41 |

Ultrasonographic parameters

| Variable | All (n = 46) | DVT regression group (n = 29) | DVT non-regression group (n = 17) | P value |
|----------|-------------|-----------------------------|----------------------------------|--------|
| Proximal DVT (n, %) | 17 (63%) | 18 (62%) | 11 (65%) | 0.43 |
| Distal DVT (n, %) | 25 (85%) | 26 (90%) | 13 (76%) | 0.12 |
| DVT diameter pre DOACs treatment (mm) | 4.1 ± 2.1 | 4.0 ± 1.7 | 4.4 ± 2.7 | 0.30 |
| Percent regression (%) | 49 ± 31 | 70 ± 19 | 13 ± 7 | <0.001 |
| Ave. GCM diameter index (mm/m²) | 9.3 ± 1.8 | 10.2 ± 1.6 | 7.9 ± 1.1 | <0.001 |
| Ave. GCM IB index (dB) | -65.4 ± 6.6 | -67.4 ± 3.5 | -62.1 ± 4.3 | <0.001 |

Inbody parameters

| Variable | All (n = 46) | DVT regression group (n = 29) | DVT non-regression group (n = 17) | P value |
|----------|-------------|-----------------------------|----------------------------------|--------|
| Muscle mass index (kg/m²) | 24.2 ± 3.2 | 24.5 ± 3.2 | 23.7 ± 3.1 | 0.22 |
| Ave. leg muscle mass index (kg/m²) | 4.7 ± 0.9 | 4.8 ± 0.8 | 4.5 ± 1.0 | 0.14 |
| Skeletal muscle mass index (kg/m²) | 6.1 ± 1.2 | 6.2 ± 1.1 | 5.8 ± 1.2 | 0.14 |
| Body muscle mass index (kg/m²) | 10.2 ± 1.9 | 10.3 ± 2.1 | 10.0 ± 1.6 | 0.29 |
| Fat mass (kg) | 19.7 ± 8.7 | 19.7 ± 9.6 | 19.5 ± 6.8 | 0.47 |

Data are presented as number of patients (percentage), mean ± SD or median (interquartile range). DOACs high dose is a patient who initially treated with apixaban 20 mg/day for 1 week, edoxaban 60 mg/day and rivaroxaban 30 mg/day for 3 weeks. DOACs low dose is a patient who started treatment with apixaban 10 mg/day, edoxaban 30 mg/day and rivaroxaban 15 mg/day. eGFR indicates estimated glomerular filtration rate; DOACs, Direct Oral Anticoagulants; DVT, deep vein thrombus; GCM, Gastrocnemius muscle; and IB, Integrated backscatter.

Figure 3. DVT diameter at baseline and follow-up in patients with DVT regression and DVT non-regression.

revealed that Ave. GCM diameter index had a significantly higher ability to detect DVT regression compared to the other variables. The Ave. GCM diameter index had the highest area under the curve (AUC) (0.90; P < 0.001).
The odds ratio for a 1-U increase in the predictor (e.g., mm, kg and kg/m²). OR indicates odds ratio; CI, confidence interval, other abbreviations as in Table I.

### Discusions

The present study investigated the association of factors influencing DVT regression by DOACs. Specifically, DVT regression correlated with Ave. GCM diameter index and Ave. GCM IB index. IB value is also used to predict DVT regression, but clinically, measuring GCM diameter alone is sufficient. Ave. GCM diameter index was independently associated with DVT regression. Of note, Ave. GCM diameter index had the highest prediction ability compared to several clinical factors. To the best of our knowledge, the present study is the first to confirm Ave. GCM diameter index usefulness in predicting DVT regression, following adjustment with several clinical factors.

**DVT regression predictors:** Reduced lower leg muscle pumping action is likely to cause DVT formation due to blood stasis. Sarcopenia reduces muscle strength as it influences the elderly individuals’ motor function. Unlike inactive muscle atrophy, which exhibits no decrease in the number of myofibers and comprises of predominantly atrophy of the slow-twitch (type I) fibers (e.g., muscular dystrophy), sarcopenia is characterized by selective atrophy of fast-twitch (type II) fibers and a decrease in the number of myofibers due to decreased muscle regeneration ability. The gastrocnemius and soleus muscles are present in the lower leg; the GCM is known to have more fast-twitch muscles than the soleus muscle. Therefore, Ave. GCM diameter index may demonstrate change asso-
Figure 4. Receiver operating characteristic curve analysis of measured using several parameters for predicting DVT regression, were constructed and compared using receiver operating characteristic analysis. AUC indicates area under the curve; and GCM, gastrocnemius muscle.

Figure 5. Receiver operating characteristic curve analysis of GCM diameter index measured using ultrasonography for evaluation of DVT reduce. To evaluate the ability of GCM diameter index measured using ultrasonography to predict DVT reduction in addition to clinical variables, three models (model 1: clinical risk factors alone; the basic model; model 2: model 1 plus Ave. GCM IB value index; and model 3: model 1 plus Ave. GCM diameter index) were constructed and compared using ROC curve analysis.

associated with sarcopenia. In addition, Inbody calculated muscle mass for the entire lower limb, including the thigh which comprises most of the leg muscles, suggesting no difference between the two groups. The GCM is a good
Figure 6. Incremental prognostic value of ultrasonographic parameters when added to clinical data. This figure illustrates the global chi-square of sequential Cox models incorporating several clinical parameters. DOACs indicates direct oral anticoagulants; and GCM, gastrocnemius muscle.

marker for the early detection of muscle fat deposition by sarcopenia.

**Differences in predictive power for DVT regression:** The measurement of IB index by ultrasonography and GCM diameter were found to be promising indicators for predicting DVT regression. As the IB index measures backscattered signals, the reflection angle from the tissue must be taken into consideration; therefore, failure to do so may increase examiner error. In addition, it can only be measured with limited equipment. The IB value varies between the equipment, even from the same manufacturer, as the calculation process is different. Therefore, IB index measurement is difficult to use clinically. By contrast, Ave. GCM diameter has small error between examiners and can be measured with any equipment. It is convenient, error-free, and does not vary between equipment; therefore, it is a useful marker to predict DVT regression in clinical practice.

**Advantage of ultrasonography:** Ultrasonography is an indispensable test for the diagnosis of DVT and determination of therapeutic effects, and is widely used in routine practice. The decrease in muscle pumping effect, responsible for venous return, may cause a change in muscle mass, and muscle quality may be involved in the DVT regression effect. Traditionally, the muscle cross-sectional area method of computerized tomography (CT) and magnetic resonance imaging (MRI) has been the standard for evaluating reduced muscle mass and intramuscular fat mass. However, examination length and the specific equipment required make it difficult to implement easily. Ultrasonography is also widely employed in the fields of orthopedics and musculoskeletal health, and correlation between CT and MRI has been reported for muscle thickness measured in ultrasonography images. Therefore, it is considered useful to measure GCM diameter along with DVT diagnosis.

**Clinical implications:** Predicting DVT’s therapeutic effect is important in clinical practice. Remnant DVT may lead to a higher risk of pulmonary embolism, and anticoagulation therapy must be continued. The remaining thrombus causes post-thrombotic syndrome, which is known to lower patient quality of life. If the thrombus is unlikely to regress following anticoagulation therapy, longer-term treatment is required. If there is a high possibility of regression, aggressive anticoagulation therapy can be initiated. Predicting the effect of thrombus regression, as described above, is important in determining the treatment protocol and is considered beneficial for treatment.

**Limitations:** The present study had several limitations. First, it was a single-center prospective study with a small sample size. Therefore, subgroup analysis was limited. Secondly, the long-term results of >90 days remain to be
elucidated. Specifically, long-term observation was not performed past the recommended DVT treatment period. Also, it was impossible to consider bleeding events since no major bleeding events, which resulted in discontinuation of therapy, were observed. Thirdly, DVT was diagnosed by ultrasound examination only. Therefore, the existence of DVT was not confirmed via other modalities (e.g., contrast-enhanced computed tomography). Finally, the DVT length was not measured. However, the short axis compression method is the golden standard for DVT diagnosis. Thus, we considered the diagnostic accuracy of DVT maintained.

Conclusions
Ave. GCM diameter index and Ave. GCM IB index are associated with DVT regression. In particular, Ave. GCM diameter index can be employed widely in the clinical setting, as it is simple and independent of examiner variation. Follow-up of the diameter of the GCM during DVT treatment offers potential for improving treatment efficacy.

Disclosure
Conflicts of interest: The authors have no conflicts of interest to disclose.

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Supplemental Files
Supplemental Figures 1, 2
Please see supplemental files; https://doi.org/10.1536/ihj.20-032