Ultrasound assessment of sarcopenia in patients with rheumatoid arthritis

Takeshi Yoshida, Yoshitaka Kusun, Naoko Takamatsu, Taiki Nozaki, Masataka Inoue, Hiroyuki Nodera, Jemima Albayda and Yuishin Izumi

Department of Rheumatology, Chikamori Hospital, Kochi, Japan
Department of Neurology, Tokushima University School of Medicine, Tokushima, Japan
Department of Radiology, St. Luke’s International Hospital, Tokyo, Japan
Faculty of Nursing, University of Kochi, Kochi, Japan
Department of Neurology, Tenri Hospital, Kyoto, Japan
School of Medicine, Division of Rheumatology, Johns Hopkins University, Baltimore, MD, USA

ABSTRACT

Objectives: To evaluate the efficacy of ultrasound (US) as a diagnostic tool for sarcopenia in patients with rheumatoid arthritis (RA).

Methods: Female RA patients aged >50 years and matched controls were cross-sectionally assessed. Sarcopenia was diagnosed based on the 2019-updated Asian Working Group for Sarcopenia definition. The cross-sectional area (CSA) and echo intensity (EI) of the biceps brachii, rectus femoris, and EI of the vastus lateralis were examined bilaterally. Correction for subcutaneous fat and calculation of the corrected EI (rcEI) were performed. We performed logistic regression using both muscle rcEI and CSA with receiver operating curve analysis to evaluate the discriminative performance per muscle group.

Results: Seventy-eight consecutive RA patients and 15 age-and sex-matched controls were assessed. Sarcopenia was diagnosed in 34 RA patients (43.6%). The rcEI of examined muscles were significantly higher, whereas CSA were significantly lower in sarcopenic RA patients than in non-sarcopenic patients and matched controls. The combined discriminative performance of rcEI and CSA was superior to those of rcEI or CSA alone.

Conclusions: This study suggests the use of US for the diagnosis of sarcopenia in RA patients. The diagnostic performance increases when both echogenicity and CSA are considered together rather than individually.

KEYWORDS: Sarcopenia; rheumatoid arthritis; ultrasound

Introduction

Sarcopenia is a progressive and generalised skeletal muscle disorder causing accelerated loss of muscle mass and function. It is associated with adverse outcomes, including falls, functional decline, frailty, and mortality [1]. While commonly an age-related condition, it is also associated with a number of medical conditions, including rheumatoid arthritis (RA) [1, 2]. RA is a chronic inflammatory joint disease characterised by progressive joint destruction and systematically increased levels of inflammatory cytokines, such as IL-1β, IL-6, and TNF-α [3, 4]. A sedentary lifestyle associated with joint damage exposes RA patients to a higher risk of decline in physical performance. Chronically elevated inflammatory cytokines cause a reduction in muscle mass and muscle function, resulting in an increased risk of sarcopenia in this population [1, 2, 5–7]. Thus, early detection and treatment are of paramount importance.

The current definition of sarcopenia reports muscle composition as measured by dual energy X-ray absorptiometry (DEXA) or bioimpedance analysis (BIA) [8]; however, the importance of changes in muscle quality have also been suggested [8–10]. Imaging modalities such as ultrasound (US) or magnetic resonance imaging can detect and analyse the changes in muscle mass associated with aging and the accompanying myosteatosis, which is an increase in intramuscular adipose tissue [9, 11–14]. US has several unique characteristics that are advantageous in routine clinical setting – easy availability in the clinic, simultaneous evaluation of arms and legs, non-invasive nature, and no contraindications – and make this modality a promising diagnostic tool for patients with sarcopenia. However, US also has its challenges, including a need for correction of the measured echo intensity (EI) by overlying subcutaneous fat thickness for accurate quantification of intramuscular fat [12, 15].

The European Working Group on Sarcopenia in Older People has reported the importance of US in the evaluation of sarcopenia. However, few studies have documented its efficacy [10, 16–18]. Further research is needed for patients with rheumatic disorders, other varying conditions and health status.

In this study, we quantitatively measured EI and cross-sectional area (CSA) of skeletal muscles in RA patients with or
without sarcopenia, and their matched controls. We evaluated the potential usefulness of US assessment of skeletal muscle for diagnosing sarcopenia in a routine rheumatology clinic setting.

Materials and methods

Patients

We conducted a single-centre, cross-sectional study in patients with RA who visited the rheumatology clinic at Chikamori Hospital from January 2020 to February 2021. We consecutively included female RA patients ≥50 years of age who fulfilled the 2010 ACR/EULAR RA Classification Criteria [19]. Patients who were not ambulatory due to coexisting neuromuscular or orthopedic disorders were excluded from the study. Similarly, we did not include patients with significant knee or ankle arthritis who could not participate in the physical performance tests. Individuals with dementia and those having difficulty comprehending the study protocol were also excluded. Age-and sex-matched controls without rheumatologic, neuromuscular, or cognitive disorders were included.

This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board (IRB) of Chikamori Hospital (IRB number 119-303). Written information was given to all participants and an option to opt-out of the study was provided; this information was published on the website of Chikamori hospital.

Clinical assessment

Clinical assessment was conducted by two board-certified rheumatologists (T.Y. and Y.K.). We obtained the following data: age, sex, body mass index (BMI), disease duration, disease activity (clinical disease activity index [CDAI]) [20], health assessment questionnaire-disability index (HAQ-DI) [21], rheumatoid factor, anti-cyclic citrullinated peptide antibody, history of steroid use, conventional synthetic disease-modifying antirheumatic drugs, biologic DMARDs (bDMARDs), and targeted synthetic DMARDs (tsDMARDs), as well as coexisting medical conditions.

Physical function and measurement of body composition

A trained research assistant conducted physical tests, such as walking speed and the chair stand test, prior to performing body composition analysis. Basic anthropometric measurements such as weight, height, abdominal circumference were also obtained. Sarcopenia was diagnosed based on the 2019 updated Asian Working Group for Sarcopenia consensus, which defines sarcopenia as age-related loss of muscle mass, decreased muscle strength, and/or decreased physical performance [22]. Since the handgrip strength is often difficult to assess for patients with active arthritis [2, 8], we did not perform it for determining muscle strength. Instead, the chair stand test and walking speed were selected as primary measures for the diagnosis of sarcopenia.

Body composition was assessed by direct segmental multifrequency bioimpedance analysis (DSM-BIA) (InBody770, InBody Co., Ltd., Seoul, Korea) [23]. Appendicular skeletal muscle mass (ASM) was calculated as the sum of skeletal muscle mass in the arms and legs. Skeletal muscle index (SMI) was calculated using the equation ASM/height2 (kg/m²). All participants were advised to avoid eating and drinking for at least 3 hours prior and did not receive intravenous fluids for at least 12 hours before examination.

US study

All US studies were performed by the same person (T.Y.) who had at least 3 years of experience in muscle ultrasonography at the start of this study. For US analysis, we used the LOGIQ S8 (GE, USA; 4–15 MHz, linear-array transducer) equipment. All US studies were conducted under the same settings (frequency: 9.0 MHz; gain: 50 dB; depth: 4.0 cm for arms and 5.0 cm for legs, dynamic range: 66 dB). Sensitive time control was set in a neutral position. During the examination, patients were asked to lay in the supine position with their elbow and knee joints in an extended position [24]. For each patient, we obtained axial images of the biceps brachii (BB), vastus lateralis (VL), and rectus femoris (RF) at a predetermined position (BB: at the point of maximal bulk that was identified by inspection and palpation, VL; from the lateral side of the thigh at the midpoint between the anterior superior iliac spine and superior edge of the patella, RF; anterior thigh at the same level as that of VL) bilaterally [24]. Minimal pressure was applied to the overlying skin during the examination (Figure 1).

On measuring US EI, regions of interest (ROI) were manually drawn along hyperechoic rim of the epimysium using ImageJ, an image processing software, by one author (T.Y.), who was blinded to the results of body composition analysis and physical performance. For each muscle, the mean EI (BB, RF, VL) and CSA (BB, RF) were calculated by averaging the values of the two muscles on each side. Arbitary unit (A.U.) was used for the measurement of EI and CSA was measured as the number of pixels within the ROI. We did not measure CSA of VL because the transverse diameter of this muscle was larger than the probe size.

Regarding reproducibility of US images, previous reports have shown high intra- and inter-rater reliability of muscle thickness and EI measurement [25]. In this study, we assessed inter- and intra-rater reliability of muscle US using the machine in our institution. Ten healthy participants (mean age 35.6 ± 8.2 years, nine women) were recruited. A rheumatologist with more than 3 years of experience in muscle US (T.Y., examiner A) and a radiologist with more than 10 years of experience in musculoskeletal US (examiner B) performed US analysis of the right BB. Two axial images were obtained, and the EI and CSA were measured in each patient. Intra- and inter-rater reliabilities were calculated using intraclass correlation coefficients (ICCs). ICC values of <0.40, 0.40–0.59, 0.60–0.74, and >0.75 were considered poor, fair, good, and excellent, respectively.

As shown in Supplementary Figure S1 in detail, appropriate correction of measured EI for subcutaneous fat was performed. Since the overlying subcutaneous fat decreases muscle EI, measured EI was corrected for subcutaneous fat thickness as reported by Young et al. [12] (Figure 2). Fifteen RA patients with optimal subcutaneous fat over the examined muscles were selected for the analysis. In each patient, five or six images were obtained for BB, VL, and RF on the right side (Figure 2). Muscle EI was measured, and linear regression analysis was performed in each patient to calculate the mean regression coefficient (β1) of...
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Figure 1. US image of biceps brachii (A, D), vastus lateralis (B, E), and rectus femoris (C, F).

(A–C) A 60-year-old female RA patient with normal physical function and muscle volume. (D–F) An 84-year-old female RA patient with sarcopenia. The sarcopenic patient showed higher muscle EI and decreased CSA. CSA: cross sectional area; EI: echo intensity; RA: rheumatoid arthritis; US: ultrasound.

Figure 2. Measurement of subcutaneous fat thickness.

(A, B) In each muscle image, we measured subcutaneous fat thickness at the middle point of a picture. The pressure of the examiner’s probe was slightly changed to obtain images with different subcutaneous fat thickness (double headed arrows). Efforts were made not to change muscle morphology. In each patient, 5–6 images were obtained on the right side.

BB, VL, and RF. Assuming that a patient had no subcutaneous fat, corrected muscle EI was calculated by adding a product of $\beta_1$ and subcutaneous fat thickness to raw muscle EI.

$$\text{Corrected } EI = \text{raw } EI + \beta_1 \times \text{subcutaneous fat thickness}$$

RcEI is considered to better represent the amount of intramuscular fat associated with sarcopenia by optimally removing the effect of subcutaneous fat.

Statistical analysis

Most statistical analyses were performed using EZR, a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [26]. The Mann–Whitney U-test was used to compare numerical variables, including muscle EI and CSA measured by US. Spearman’s rank correlation coefficient was used to measure the correlation among US test results, physical performance, and muscle mass. IBM SPSS Statistics version 21 (IBM, NY, USA) was used to perform logistic regression using both muscle EI and CSA with receiver operating characteristic (ROC) curve analysis to evaluate the discriminative test quality per muscle group. A $p$ value of <0.05 was determined as the cutoff for statistical significance.

Results

We evaluated 78 RA patients and 15 age- and sex-matched controls. Table 1 displays the baseline characteristics of the 78 patients with RA. Thirty-four patients (43.6%) were found to have sarcopenia. Compared to the non-sarcopenia group, patients in the sarcopenia group were older, had higher CDAI and HAQ-DI scores, and used bDMARDs or tsDMARDs more often.

The results of the physical function examination and body composition analysis are shown in Table 2. As expected, patients with sarcopenia had low BMI and a small abdominal circumference, and reduced physical function (walking speed, chair stand test). Measures of skeletal muscle mass,
including SMI, were significantly reduced in the sarcopenia group. Osteoporosis was also more prevalent in the group with sarcopenia.

Additionally, in the US study, mean rcEI of BB, VL, and RF were significantly increased in sarcopenia group compared to the non-sarcopenia group (BB: 92.0 A.U. vs 79.2 A.U., p = 0.005; RF: 100.0 A.U. vs 89.9 A.U., p = 0.01; VL: 86.9 A.U. vs 78.4 A.U., p = 0.03; Figure 3(A–C)). Mean CSA of BB and RF were significantly decreased in the sarcopenia group (BB: 8.7×10E4 pixels vs 1.1×10E5 pixels, p = 0.005; RF: 5.9×10E4 pixels vs 7.5×10E4 pixels, p < 0.001; Figure 3(D,E)). Similarly, when compared to age- and sex-matched controls, sarcopenic RA patients also showed significantly higher rcEI and smaller CSA in all examined muscles (Supplementary Figure S2). Regarding reproducibility of US test results, the ICC of the intrarater reliability for the EI and CSA were 0.79 and 0.98 and 0.96 for examiner A and 0.99 and 0.96 for examiner B, respectively. The ICC of the interrater reliability for the EI and CSA were 0.73 and 0.99, respectively. Overall, the results showed good-excellent reproducibility of the US tests.

There was a significant correlation between rcEI and gait speed (RF: r = 0.29, p = 0.01), rcEI and SMI (RF: r = −0.35, p = 0.002; VL: r = −0.24, p = 0.04), CSA and gait speed (BB: r = 0.34, p = 0.0025; RF: r = 0.51, p < 0.001), and CSA and SMI (BB: r = 0.7, p < 0.001; RF: r = 0.63, p < 0.001) (Figure 4).

Table 1. Baseline characteristics of patients.

<table>
<thead>
<tr>
<th></th>
<th>Sarcopenia</th>
<th>Non-sarcopenia</th>
<th>p value</th>
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<tbody>
<tr>
<td>Total number</td>
<td>34</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>Age (years, median [IQR])</td>
<td>72.5 (69–79.75)</td>
<td>64.0 (59–72.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>DM (%)</td>
<td>9 (26.5)</td>
<td>10 (22.7)</td>
<td>0.79</td>
</tr>
<tr>
<td>Thyroid diseases (%)</td>
<td>4 (11.8)</td>
<td>11 (25.6)</td>
<td>0.16</td>
</tr>
<tr>
<td>Duration (months, median [IQR])</td>
<td>54 (27–144)</td>
<td>60 (19–108)</td>
<td>0.45</td>
</tr>
<tr>
<td>ACPA (%)</td>
<td>25 (73.5)</td>
<td>34 (77.3)</td>
<td>0.79</td>
</tr>
<tr>
<td>RF (%)</td>
<td>28 (82.4)</td>
<td>41 (93.2)</td>
<td>0.17</td>
</tr>
<tr>
<td>CDAI (median [IQR])</td>
<td>4.45 (2.13–6.38)</td>
<td>2.25 (0.5–3.85)</td>
<td>0.005</td>
</tr>
<tr>
<td>HAQ-DI (median [IQR])</td>
<td>0.38 (0.125–1.22)</td>
<td>0 (0–0.25)</td>
<td>0.000008</td>
</tr>
<tr>
<td>Current MTX use (%)</td>
<td>18 (52.9)</td>
<td>30 (68.1)</td>
<td>0.24</td>
</tr>
<tr>
<td>Current SSZ use (%)</td>
<td>18 (52.9)</td>
<td>28 (63.6)</td>
<td>0.36</td>
</tr>
<tr>
<td>Current GC use (%)</td>
<td>8 (23.5)</td>
<td>5 (11.4)</td>
<td>0.22</td>
</tr>
<tr>
<td>Current bDMARD/tsDMARD use (%)</td>
<td>21 (61.8)</td>
<td>16 (36.4)</td>
<td>0.039</td>
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</table>

Table 2. Physical function and body composition measures.

<table>
<thead>
<tr>
<th></th>
<th>Sarcopenia</th>
<th>Non-sarcopenia</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number</td>
<td>34</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m², median [IQR])</td>
<td>21.5 (20.03–23.47)</td>
<td>23.9 (20.93–25.75)</td>
<td>0.008</td>
</tr>
<tr>
<td>Abdominal circumference (cm, median [IQR])</td>
<td>78 (73.0–84.0)</td>
<td>81 (75.75–89.5)</td>
<td>0.067</td>
</tr>
<tr>
<td>Body fat mass (%)</td>
<td>17.4 (12.98–22.33)</td>
<td>19.95 (14.35–25.9)</td>
<td>0.32</td>
</tr>
<tr>
<td>SARC-F (median [IQR])</td>
<td>2.5 (1–4)</td>
<td>1.0 (0–2)</td>
<td>0.002</td>
</tr>
<tr>
<td>Gait speed (m/sec, median [IQR])</td>
<td>0.8 (0.55–0.86)</td>
<td>1.02 (0.88–1.15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chair stand test (sec, median [IQR])</td>
<td>12.2 (9.84–14.39)</td>
<td>9.37 (7.8–11.14)</td>
<td>0.008</td>
</tr>
<tr>
<td>SMM (kg, median [IQR])</td>
<td>19.5 (18.55–21.16)</td>
<td>16.2 (14.63–16.95)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ASM (kg, median [IQR])</td>
<td>11.66 (10.8–12.39)</td>
<td>14.94 (13.57–16.19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SM (kg/m², median [IQR])</td>
<td>5.15 (4.83–5.4)</td>
<td>6.1 (5.8–6.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Osteoporosis (%)</td>
<td>19 (55.9)</td>
<td>18 (87.2)</td>
<td>&lt;0.001</td>
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</table>

Logistic regression and ROC curve analysis with combined rcEI and CSA of BB and RF showed comparably high areas under the ROC curve (AUC) of 0.851 (95% CI, 0.765–0.938) and 0.853 (95% CI, 0.766–0.94), respectively (Figure 5). Their discriminative performance was superior to that of rcEI alone (AUC = 0.694 and 0.665 for BB and RF, respectively) and CSA alone (AUC = 0.809 and 0.776 for BB and RF, respectively). Compared to the diagnostics using raw EI, those using rcEI showed comparable discriminative performance; for the assessment of BB, the AUC was 0.68 (95% CI, 0.557–0.802) and 0.682 (95% CI, 0.562–0.803) for raw EI and rcEI, respectively; for RF, the AUC was 0.723 (95% CI, 0.608–0.838) and 0.673 (95% CI, 0.551–0.795) for raw EI and rcEI, respectively.

Discussion

This study reports a significantly increased rcEI and decreased CSA in sarcopenic RA patients compared to both non-sarcopenic RA patients and age- and sex-matched controls. There was a significant correlation among the US findings, physical performance, and skeletal muscle mass as assessed by DSM-BIA. The combined diagnostic performance of rcEI and CSA was superior to that of rcEI or CSA alone. We suggest that US is useful for diagnosing sarcopenia in the RA population, and the combined assessment of echogenicity and CSA
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In an aging population, rheumatologists are facing new challenges not only to treat the targeted disease activity, but also to help patients prevent sarcopenia and maintain their activities of daily living by providing appropriate patient education, lifestyle modifications, and fitness advice [8, 27]. Since US is routinely used in clinics, muscle sonography can be added as a simple screening tool in the ‘at-risk’ group [28]. Patients can visually appreciate the health status of their muscles, which would aid in promoting a discussion between rheumatologists and patients.

US can sensitively measure myosteatosis that is an important marker of muscle quality and is accompanied with decreased muscle strength, although relatively few studies have addressed the efficacy of US in quantitatively analysing the muscle EI in sarcopenia [10, 12, 13, 29]. Because conventional diagnostic measures of sarcopenia such as DEXA and BIA only concern muscle mass, implementation of practical imaging tests of muscle quality was long awaited. Our study is the first to demonstrate that simultaneous assessment of muscle echogenicity and muscle CSA improved the discriminative performance of US in RA patients with or without sarcopenia. The efficacy of the combined assessment of echogenicity and muscle thickness by US has also been reported in patients with inflammatory myopathies [30]. Mounting evidence suggests that US can provide accurate and reliable estimates of BIA- or DXA-derived skeletal muscle mass [29]. The potential role of increased intramuscular fat in muscle weakness is termed as ‘lipotoxicity’ [7]. Inflammation associated with RA promotes increased intramuscular adiposity further aggravating the pathophysiology cascade [5, 7]. Thus, in patients with RA, US-based muscle quality assessment may be of particular relevance for diagnosing sarcopenia.

In our patients with RA, rcEI and raw EI showed comparable discriminative performances. When measuring US EI with grey-scale analysis using imaging software, appropriate correction for subcutaneous fat thickness is suggested [12, 15]. Young et al. reported the quantitative measurement of intramuscular fat by calculating corrected EI from raw EI and subcutaneous fat thickness [12]. Nijboer-Oosterveld et al. created an equation for normal EI values according to age, height, weight, and subcutaneous tissue thickness [15]. Contrary to their expectations, the higher the subcutaneous thickness, the higher was the EI. This phenomenon was explained by increased intramuscular fat infiltration in the obese. In RA patients, the correlation between subcutaneous thickness and corrected EI may differ from that of normal controls because systemic inflammation and treatments such as steroids and DMARDs may differently affect systemic and intramuscular adiposity [31, 32].

The present study has certain limitations. First, because of its cross-sectional study design, we could not evaluate changes in body composition and its correlation with US parameters. Future studies should address this to enhance the efficacy of US in routine clinical practice. Second, we performed a 4 m-walking speed instead of a 6 m test. Although 4 m-walking speed is also a validated, internationally accepted test [8] and different walking distances do not significantly alter walking speed [33], this slight difference from the original protocol may have influenced the prevalence of sarcopenia and diagnostic performance of US in our results. Third, because calculation of rcEI requires complex analysis, it may not be applicable in daily clinical practice. Although $\beta_1$ is a fixed value if the US machine and all the settings are kept consistent [12], $\beta_2$ value may vary among different group of patients and healthy controls. We minimised this potential variation among RA patients by recruiting only elderly...
female population. However, we acknowledge that different β2 values would be applied for RA patients with different background, such as male patients aged <50 years. Instead, as we observed comparative discriminative performance of raw EI as rcEI, it can be used for this purpose. Alternatively, automated diagnosis using deep learning would be the to overcome...
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Figure 5. ROC curve analysis of US study of BB (A) and RF (B).

Combined rcEI and CSA of BB and RF showed comparably high discriminative capacity and were superior to rcEI or CSA only. AUC: area under the ROC curve; BB: biceps brachii; CSA: cross-sectional area; rcEI: recorrected echo intensity; RF: rectus femoris; VL: vastus lateralis; US: ultrasound.

this issue [34]. Fourth, CSA of VL was not measured because of larger size of this muscle compared to US probe. Panoramic images would be warranted to fully visualise large muscles as VL.

Conclusion

Our findings demonstrate that US is useful for the assessment of sarcopenia in the RA population. The combined predictive efficacy of echogenicity and CSA was greater than the assessment of echogenicity or CSA alone for the diagnosis of sarcopenia.

Supplementary data

Supplementary data is available at Modern Rheumatology online.

Conflict of interest

None declared.

Funding

None declared.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References


