

Original article

Muscle involvement in systemic lupus erythematosus: multimodal ultrasound assessment and relationship with physical performance

Andrea Di Matteo ¹, Gianluca Smerilli ¹, Edoardo Cipolletta ¹, Richard J. Wakefield², Rossella De Angelis¹, Anna Maria Risa¹, Fausto Salaffi¹, Sonia Farah¹, Catalina Villota-Eraso³, Vincenzo Maccarrone¹, Emilio Filippucci¹ and Walter Grassi¹

Abstract

Objectives. The objectives of this study were (1) to explore US findings for muscle mass, muscle quality and muscle stiffness in SLE patients and healthy subjects; (2) to investigate the relationship between the US muscle findings and physical performance in SLE patients and healthy subjects.

Methods. Quadriceps muscle thickness was used for assessment of muscle mass, muscle echogenicity (using a visual semi-quantitative scale and grayscale analysis with histograms) for assessment of muscle quality, and point shear-wave elastography (SWE) for assessment of muscle stiffness in 30 SLE patients (without previous/current myositis or neuromuscular disorders) and 15 age-, sex- and BMI-matched healthy subjects. Hand grip strength tests and short physical performance battery (SPPB) tests were carried out in the same populations.

Results. No difference was observed between SLE patients and healthy subjects for quadriceps muscle thickness (35.2 mm \pm s.d. 6.8 vs 34.8 mm \pm s.d. 6.0, respectively, $P=0.79$). Conversely, muscle echogenicity was significantly increased in SLE patients (visual semi-quantitative scale: 1.7 \pm s.d. 1.0 vs 0.3 \pm s.d. 0.5, respectively, $P<0.01$; grayscale analysis with histograms: 87.4 mean pixels \pm s.d. 18.8 vs 70.1 mean pixels \pm s.d. 14.0, respectively, $P<0.01$). Similarly, SWE was significantly lower in SLE patients compared with healthy subjects {1.5 m/s [interquartile range (IQR) 0.3] vs 1.6 m/s (IQR 0.2), respectively, $P=0.01$ }. Muscle echogenicity was inversely correlated with grip strength (visual semi-quantitative scale, $Rho: -0.47$, $P=0.01$; grayscale analysis with histograms, $Rho: -0.41$, $p<0.01$) and SPPB (visual semi-quantitative scale, $Rho: -0.50$, $P<0.01$; grayscale analysis with histograms $Rho: -0.46$, $P<0.01$).

Conclusions. US assessment of muscle echogenicity and stiffness is useful for the early detection of muscle involvement in SLE patients.

Key words: muscle, ultrasound, muscle mass, muscle echogenicity, muscle stiffness, shear-wave elastography, muscle strength, sarcopenia, systemic lupus erythematosus, physical performance

Rheumatology key messages

- The role of US in the assessment of muscle involvement in SLE patients has scarcely been explored.
- US evaluation of muscle echogenicity and stiffness, but not US muscle mass, can discriminate between SLE patients and healthy subjects.
- Multimodal US may improve the early identification of SLE patients with reduced muscle strength and physical performance.

¹Polytechnic University of Marche, Rheumatology Unit, Department of Clinical and Molecular Sciences, 'Carlo Urbani' Hospital, Jesi, Ancona, Italy, ²Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK and ³Department of Rheumatology, Universidad de la Sabana, Chia, Colombia
Submitted 17 November 2021; accepted 21 March 2022

Correspondence to: Andrea Di Matteo, Polytechnic University of Marche, Department of Clinical and Molecular Sciences, Rheumatology Unit, 'Carlo Urbani' Hospital, Via Aldo Moro 25, 60035 Jesi, Ancona, Italy. E-mail: andrea.dimatteo@hotmail.com

Introduction

The musculoskeletal (MSK) system is frequently involved in patients with SLE [1]. The spectrum of MSK manifestations in SLE is broad and heterogeneous; SLE can affect the joints, tendons, muscles and bones [2]. In recent years, several imaging studies, especially of US and MRI, have explored the prevalence and clinical impact of MSK manifestations in patients with SLE [3, 4]. Most of these studies have focused on joints and soft tissues, while muscles have been poorly investigated [5, 6].

Muscle involvement in SLE has been traditionally linked to two main conditions: myositis (an inflammatory muscle disorder) and drug-induced myopathy [7, 8]. The clinical and imaging findings in SLE myositis are similar to those observed in PM, while the histologic findings are often less pronounced in SLE patients [9]. In a biopsy study on 55 unselected patients with SLE, lymphocytic vasculitis, myositis, and type II fibre atrophy were significantly increased in SLE patients in comparison with healthy controls [10]. Steroid-induced myopathy is a well-known complication of long-term steroid use in SLE patients. In this condition, muscle enzymes (e.g. creatine phosphokinase) are usually normal, while muscle biopsy may reveal type II atrophy, with less impact on type I or slow-twitch muscle fibres, without evidence of inflammation or necrosis [9]. The potential value of imaging for the diagnosis of steroid-induced myopathy has scarcely been investigated [11].

Interestingly, recent studies have identified other pathological pathways that may potentially lead to muscle abnormalities (i.e. muscle loss, changes in muscle tissue composition, and reduced muscle strength) in patients with autoimmune or inflammatory conditions, mainly RA, but also SSc and SpA [12]. These pathological pathways may encompass physical inactivity, chronic inflammation (i.e. production of inflammatory cytokines, such as TNF- α or IL-6), reduced growth factor levels [e.g. insulin-like growth factor 1 (IGF-1)], and muscle tissue degradation secondary to cellular metabolic alterations (e.g. NF-kB pathway driven) [13].

The deterioration of skeletal muscle represents the organic substrate of sarcopenia, a muscle disease characterized by loss of muscle mass and strength, which is strongly associated with an increased risk of adverse outcomes, such as falls, frailty, fractures, hospitalization and mortality [14]. Sarcopenia is characterized by changes in muscle composition, such as marked fat and fibrous tissue infiltration, and alterations in innervation [15]. The early identification of muscle abnormalities in patients with rheumatic conditions (ideally before the development of an overt status of sarcopenia or cachexia) may raise important implications for the management of these patients (e.g. the adoption of regular exercise, use of medication and supplements) [16].

In this context, imaging has a potential key diagnostic role. CT, DXA and MRI are regarded as the reference tools for the evaluation of muscle changes. However, their use in clinical practice is limited by feasibility

aspects, such as poor availability, cost and, in the case of CT and DXA, consideration of patient exposure to ionizing radiation [17, 18]. US can depict muscle anatomical details and it has been shown to be reliable in the detection of quantitative (i.e. reduced muscle mass/thickness) and qualitative muscle changes (i.e. increased muscle echogenicity due to fatty replacement/fibrosis of muscle tissue) in patients with or at risk of sarcopenia, such as elderly patients and patients with neuromuscular or rheumatic disorders [19, 20]. In addition, by evaluating muscle stiffness, US shear-wave elastography (SWE) is emerging as a promising tool for the assessment of muscle physiological and biomechanical status [21].

To our knowledge, only one US study has investigated muscle architecture changes in patients with SLE [22]. There are no studies examining US SWE. The objectives of this study were 2-fold: first, to compare the US findings for muscle mass, muscle quality and muscle stiffness in patients with SLE (without previous or current myositis or neuromuscular disorders) and healthy subjects and, second, to investigate the correlation between the different US modalities of muscle assessment, and their relationship with the SLE patients' and healthy subjects' physical performance.

Methods

Patients

SLE patients attending the out-patient clinic of the Rheumatology Unit of the 'Carlo Urbani' Hospital, Ancona (Italy), meeting the revised ACR/SLICC 2012 criteria [23], were consecutively enrolled from February to June 2021. Age-, sex- and BMI-matched healthy subjects (i.e. volunteer staff members from the 'Carlo Urbani' Hospital) were included as controls. The exclusion criteria were: age <18 years, current/previous inflammatory myositis or neuromuscular disorders, significant arthritis that could potentially impair patients' physical performance and grip strength, and intense physical activity in the preceding 4 weeks.

Two clinical rheumatologists taking part in the study (R.D.A. and A.M.R.) collected the following data for the SLE patients: age, sex, BMI, physical exercise, current therapy with DMARDs, use of CSs, SLEDAI-2000 [24], Physician Global Assessment (0–3), SLICC-Frailty Index [25], Strength, Assistance with walking, Rising from a chair, Climbing stairs, and Falls (SARC-F) questionnaire (SARC-F \geq 4: possible sarcopenia) [26], ESR, CRP, auto-antibody profile, C3 and C4 levels, SLE clinical manifestations (e.g. MSK, mucocutaneous, vascular, neurological or renal involvement), and comorbidities. Physical exercise was self-reported by the participants of the study and expressed as number of hours of physical activity per week [27]. Participants were asked: 'Do you usually perform physical exercise such as cycling, swimming, jogging, aerobics, football, tennis or a gym workout?' Possible answers were: 'no physical activity';

'mild' ('some but <1 h'); 'moderate' (' ≥ 1 h but <3 h') and 'intense' ('3 h or more').

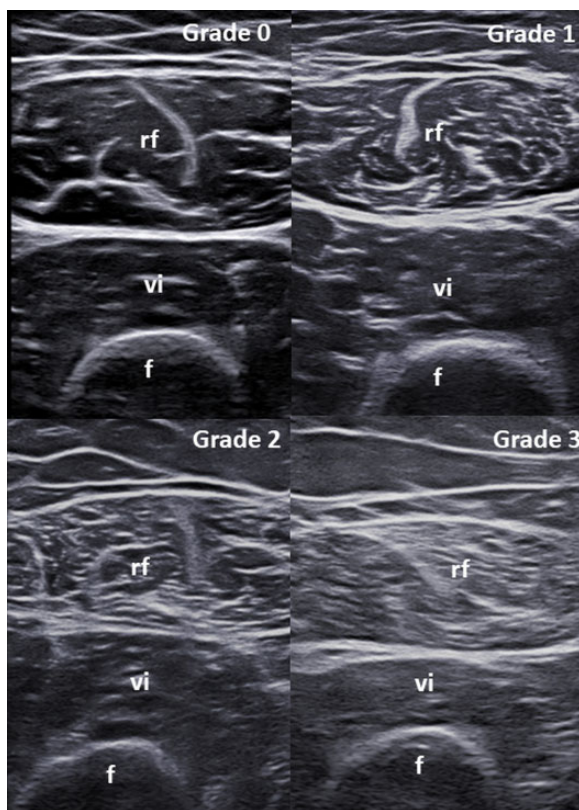
Muscle ultrasound

On the same day as the clinical evaluation, a rheumatologist with 10 years of experience in the use of MSK US (A.D.M.), blind to the SLE patients and healthy controls' demographic and clinical data, carried out the US examinations of the quadriceps muscle bilaterally.

Quadriceps muscle mass was measured adopting the anterior superior iliac spine technique. A detailed description of this technique and its interobserver reliability have recently been published by our research group [28]. The rectus femoris and vastus intermedius muscle thicknesses, as well as their sum (i.e. quadriceps muscle thickness), were measured.

The echogenicity of the rectus femoris and vastus intermedius muscles was assessed using a modified version of

Fig. 1 Modified version of the scale by Heckmatt *et al.* for the visual semi-quantitative assessment of muscle echogenicity



Grade 0 = normal (i.e. normal hypoechoic muscle); Grade 1 = mild (i.e. increased echogenicity in \leq one-third of muscle tissue); Grade 2 = moderate (i.e. increased echogenicity in $>$ one-third but \leq two-thirds of muscle tissue); Grade 3 = severe (i.e. increased echogenicity in $>$ two-thirds of muscle tissue). f: femur; rf: rectus femoris muscle; vi: vastus intermedius muscle.

the Heckmatt scale [29] developed by the current authors. This modified visual semi-quantitative scale grades muscle echogenicity from 0 to 3, where grade 0 = normal (i.e. normal hypoechoic muscle), 1 = mild (i.e. increased echogenicity in \leq one-third of muscle tissue), 2 = moderate (i.e. increased echogenicity in $>$ one-third but \leq two-thirds of muscle tissue) and 3 = severe (i.e. increased echogenicity in $>$ two-thirds of muscle tissue) (Fig. 1).

Echo intensity was also determined as mean pixel grayscale intensity in the muscle by an independent rheumatologist (V.M.), blind to the clinical and sonographic data of the SLE patients and healthy subjects, using ImageJ (version 1.53e), which is a public-domain Java-based image processing and analysis program. This imaging software determines the grayscale intensity in a region of interest (ROI), utilizing the histogram function. The rectus femoris and vastus intermedius muscles were selected as ROIs to determine the mean pixel grayscale intensity. The mean echo intensity was expressed in values (i.e. mean pixels) between 0 (black) and 255 (white).

Point SWE measurements were made in four distinct muscle areas and repeated three times for each muscle area evaluated (Fig. 2). The median of the three measurements for each area was recorded as SWE velocity in units of metres per second (m/s), with corresponding IQRs.

Further information regarding the US scanning protocol, including reliability assessment of muscle echogenicity and SWE, have been reported in [Supplementary Data S1](#), available at *Rheumatology* online.

Physical performance

SLE patients and healthy subjects underwent a hand grip strength test and SPPB test with an expert research assistant (S.F.). The hand grip strength was assessed using a cylindrically shaped grip device made of five force sensors (FSR-402) (Interlink Electronics, connected to an Arduino Mega 2560) [30]. Cut-offs for low grip strength indicating sarcopenia were established according to the European Working Group on Sarcopenia in Older People (EWGSOP) definitions [14]: < 27 kg for men, < 16 kg for women.

The SPPB is a well-established test for the evaluation of physical performances. SPPB scores range from 0 (worst performance) to 4 (best performance) for each test, with a score from 0 to 12 at patient level. The previously defined categories for SPPB were used: 0–3 = very low; 4–6 = low; 7–9 = moderate; > 10 = high [31].

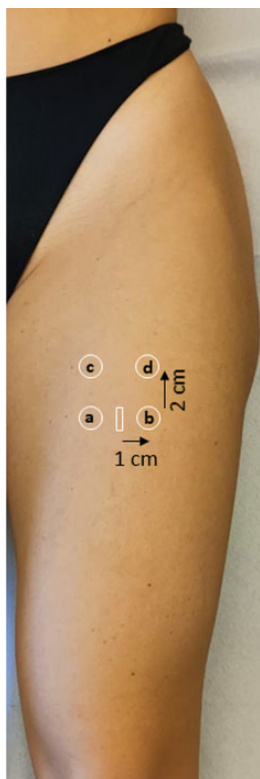
Ethical approval

This study was approved by the local ethics committee (CERM no. 155/2021). All individuals participating in the study provided written informed consent.

Statistical analysis

Continuous data were described as either medians with IQRs or means \pm S.D.s. Categorical data were described

Fig. 2 Scanning technique for the acquisition of shear-wave elastography images



Shear-wave elastography measurements were taken in four distinct muscle areas: two measurements were acquired at the level of the landmark for muscle thickness measurement (i.e. the midpoint between the ASIS and the upper pole of the patella, 1 cm medial and 1 cm lateral to the muscle central aponeurosis, 'medial' and 'lateral', respectively), and two measurements were acquired 2 cm proximally to them ('upper medial' and 'upper lateral', respectively). White rectangle: midpoint between the anterior superior iliac spine and the superior pole of the patella. a: 'medial' quadrant. b: 'lateral' quadrant. c: 'upper medial' quadrant. d: 'upper lateral' quadrant.

as frequencies and/or corresponding percentages. Continuous data were compared using the Mann-Whitney *U* test. Spearman's rank correlation was used to measure the association between the different US modalities of muscle assessment both at the thigh and patient/subject level, and between the US findings and the SLE patients' and healthy subjects' physical performance (i.e. grip strength, SPPB) at patient/subject level.

P values < 0.05 were considered significant. The US findings (i.e. muscle thickness, muscle echogenicity and SWE) and physical performance (i.e. grip strength and SPPB) were compared in SLE patients receiving and not receiving steroids. The interobserver agreement between two sonographers in the evaluation of the visual semi-quantitative scale for muscle echogenicity and SWE was calculated with

unweighted kappa and linear weighted kappa and interpreted according to Landis and Koch [32]. Reproducibility analysis for ImageJ evaluations and SWE was assessed by computing 2-way, mixed, absolute agreement intraclass correlations (ICCs) with their 95% confidence intervals. ICC values can range from 0 (i.e. variability related to within-patient variability and error) to 1 (i.e. no within patient variability and error, perfect reliability). Statistical analysis was carried out using SPSS version 26.0.

Results

Patients

Thirty SLE patients and 15 age-, gender- and BMI-matched healthy subjects were included. The main demographic and clinical characteristics of the SLE patients and healthy subjects are reported in Table 1.

US muscle findings in SLE patients and healthy subjects

A total of 60 quadriceps muscles (i.e. 60 rectus femoris and 60 vastus intermedius muscles) and 30 quadriceps muscles (i.e. 30 rectus femoris and 30 vastus intermedius muscles) were scanned in 30 SLE patients and 15 healthy subjects, respectively.

As shown in Table 2, there was no statistically significant difference in the quadriceps muscle thickness between SLE patients and healthy subjects (35.2 mm \pm s.d. 6.8 vs 34.8 mm \pm s.d. 6.0, respectively, *P* = 0.79).

On the other hand, a significant increase in quadriceps muscle echogenicity was observed in SLE patients in comparison with healthy subjects, both by the visual semi-quantitative scale (1.7 \pm s.d. 1.0 vs 0.3 \pm s.d. 0.5, respectively, *P* < 0.01) and by grayscale analysis with histograms (mean pixels: 87.4 \pm s.d. 18.8 vs 70.1 \pm s.d. 14.0, respectively, *P* < 0.01) (see also Supplementary Fig. S1, available at *Rheumatology* online).

SWE was significantly lower in SLE patients in comparison with healthy subjects [median 1.5 m/s (IQR 0.3) vs median 1.6 m/s (IQR 0.2), respectively, *P* = 0.01] (see also Supplementary Fig. S2, available at *Rheumatology* online). Fig. 3 shows representative US muscle echogenicity and SWE in SLE patients and healthy subjects.

No significant difference was observed in the US findings for SLE patients receiving steroids vs SLE patients not receiving steroids. There was a non-significant trend for an association between increased muscle echogenicity evaluated with the visual semi-quantitative scale and for steroids use (see Supplementary Data S1, available at *Rheumatology* online).

Correlations between the various US modalities of muscle assessment

As shown in Table 3, there was a significant correlation between the two US modalities for muscle echogenicity assessment, i.e. the visual semi-quantitative scale and the grayscale analysis with histograms (*Rho*: 0.71,

TABLE 1 Demographic and clinical data for the SLE patients and healthy subjects.

	SLE patients (n = 30)	Healthy subjects (n = 15)	P-value
Age (mean ± s.d.)	45.6 ± 13.7	42.3 ± 10.8	0.64
Gender (F/M)	28/2	14/1	0.53
BMI (mean ± s.d.)	24.8 ± 5.5	23.5 ± 3.8	0.84
Physical activity (yes)	7 (23.3%)	3 (20.0%)	0.90
	Mild	0	
	Moderate	2 (13.3%)	
	Intense	1 (6.7%)	
SARC-F (mean ± s.d.)	2.2 ± 2.1	0.3 (0.2)	<0.01
	SARC-F ≥ 4	0 (0.0)	
Disease duration (mean, years, ± s.d.)	11.2 ± 8.7		
Autoantibody profile			
	ANA	30 (100%)	
	Anti-dsDNA Ab	15 (50.0%)	
	Anti-SSa Ab	12 (40.0%)	
	Anti-U1RNP Ab	10 (33.3%)	
	Anti-Sm Ab	8 (26.7%)	
	Anti-SSb Ab	4 (13.3%)	
	Anti-Ribosomal P protein Ab	2 (6.7%)	
	Anti-topo-I Ab	1 (3.3%)	
Treatment			
	HCQ	22 (73.3%)	
	MMF	8 (26.7%)	
	BEL	6 (20.0%)	
	MTX	4 (13.3%)	
	AZA	2 (6.7%)	
	RTX	1 (3.3%)	
	CSs	18 (60.0%)	
	Prednisone equivalents (mg)	6.1 ± 3.2	
Laboratory			
	Raised ESR	13 (43.3%)	
	Raised CRP	7 (23.3%)	
	Low C3 level	19 (63.3%)	
	Low C4 level	15 (50.0%)	
Clinical manifestations			
	MSK (i.e. synovitis/tenosynovitis)	24 (80.0%)	
	Mucocutaneous	16 (53.3%)	
	Renal	8 (26.7%)	
	Haematological	8 (26.7%)	
	Serositis	6 (20.0%)	
	Ocular	1 (3.3%)	
	APS	3 (10.0%)	
SLE disease activity (mean ± s.d.)			
	SLEDAI-2K	4.4 ± 3.5	
	PGA-VAS	1.1 ± 0.6	
SLICC-FI			
	<0.03: robust	1 (3.3%)	
	0.03–0.10: relatively less fit	7 (23.3%)	
	0.10–0.21: least fit	14 (46.7%)	
	>0.21: frail	8 (26.7%)	
Comorbidities			
	Diabetes	2 (6.7%)	
	Dyslipidaemia	5 (16.7%)	
	Hypertension	4 (13.3%)	
	Osteoporosis	4 (13.3%)	

Ab: antibodies; BEL: belimumab; F: female; M: male; MSK: musculoskeletal; PGA: physician global assessment; RTX: rituximab; SARC-F: strength-assistance in walking-rising from a chair-climbing stairs-falls; SLEDAI-2K: SLEDAI 2000; SLICC-FI: SLICC-Frailty Index; Sm: Smith; U1RNP: anti-RNP U1; VAS: visual analogue scale.

$P < 0.01$), and an inverse correlation between these two US modalities and SWE (Rho : -0.70 , $P < 0.01$ and Rho : -0.55 , $P < 0.01$, respectively) in SLE patients and healthy subjects. Conversely, no significant correlation between muscle thickness, muscle echogenicity (neither using the visual semi-quantitative scale nor the grayscale analysis with histograms) and SWE was found.

Physical performances and correlations with the US findings

SLE patients had lower grip strength in comparison with healthy subjects ($26.2 \pm$ s.d. 5.8 vs $32.3 \pm$ s.d. 5.1), but this difference did not reach statistical significance ($P = 0.12$). One patient with SLE (3.3%), but none of the

TABLE 2 US muscle findings in SLE patients and healthy subjects

		SLE patients (n = 30)		Healthy subjects (n = 15)		P-value
		Mean	± S.D.	Mean	± S.D.	
Muscle mass	Right (mm)					
	Rectus femoris muscle thickness	19.0	3.7	18.1	2.5	0.37
	Vastus intermedius muscle thickness	16.6	6.4	17.1	4.6	0.88
	Sum (i.e. quadriceps muscle thickness)	35.4	6.8	35.2	5.7	0.97
	Left (mm)					
	Rectus femoris muscle thickness	18.6	3.5	18.0	3.1	0.52
	Vastus intermedius muscle thickness	16.5	4.6	16.5	4.8	0.85
	Sum (i.e. quadriceps muscle thickness)	35.1	6.9	34.5	6.5	0.77
	Bilateral (mm)					
	Rectus femoris muscle thickness	18.8	3.6	18.0	2.8	0.31
Vastus intermedius muscle thickness	16.4	4.3	16.8	4.6	0.98	
Sum (i.e. quadriceps muscle thickness)	35.2	6.8	34.8	6.0	0.79	
Muscle quality (muscle echogenicity)	Visual semi-quantitative scale (0–3)					
	Right quadriceps muscle	1.6	1.0	0.2	0.4	<0.01
	Left quadriceps muscle	1.7	1.0	0.3	0.6	<0.01
	Bilateral quadriceps muscles	1.7	1.0	0.3	0.5	<0.01
	Grayscale analysis with histograms (mean pixel intensity)					
	Right quadriceps muscle	87.7	20.1	69.1	15.2	<0.01
	Left quadriceps muscle	87.1	17.8	71.1	13.2	<0.01
	Bilateral quadriceps muscles	87.4	18.8	70.1	14.0	<0.01
		Median	IQR	Median	IQR	
	Muscle stiffness	SWE (m/s)				
'Medial' (bilateral)		1.5	0.2	1.6	0.3	<0.01
'Lateral' (bilateral)		1.5	0.3	1.7	0.3	<0.01
'Upper medial' (bilateral)		1.5	0.2	1.6	0.3	<0.01
'Upper lateral' (bilateral)		1.5	0.3	1.6	0.2	<0.01
Right (patient level)		1.5	0.3	1.6	0.2	0.01
Left (patient level)		1.5	0.4	1.6	0.2	0.01
Bilateral (patient level)	1.5	0.3	1.6	0.2	0.01	

Bold font indicates a significant result. IQR: interquartile range; SWE: shear-wave elastography.

healthy subjects, had reduced grip strength according to the cut-offs for sarcopenia defined by the EWGSOP (i.e. <16 kg in females). The mean SPPB results were significantly lower in SLE patients in comparison with healthy subjects ($10.1 \pm \text{s.d. } 2.2$ vs $12 \pm \text{s.d. } 0.0$, respectively, $P < 0.01$) (see also [Supplementary Fig. S3](#), available at *Rheumatology* online).

In SLE patients and healthy subjects, there was a positive trend for an association between muscle thickness and grip strength ($Rho: 0.28, P = 0.06$), but no association between muscle thickness and SPPB ($Rho: 0.06, P = 0.70$) was observed. On the other hand, muscle echogenicity was inversely correlated with grip strength (visual semi-quantitative scale $Rho: -0.47, P = 0.01$; grayscale analysis with histograms $Rho: -0.41, P < 0.01$) and SPPB (visual semi-quantitative scale $Rho: -0.50, P < 0.01$; grayscale analysis with histograms $Rho: -0.46, P < 0.01$). No significant correlation was found between SWE and grip strength ($Rho: 0.245, P = 0.10$), but there was a positive trend for an association between

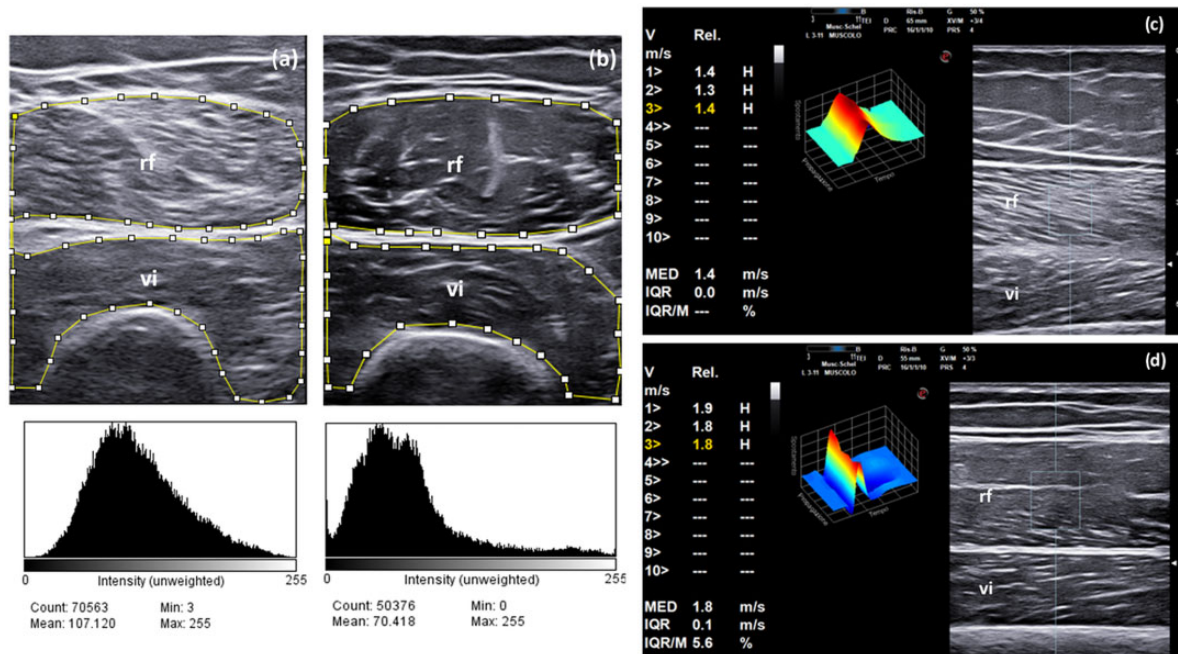
SWE and SPPB that did not reach statistical significance ($Rho: 0.28, P = 0.07$).

No significant difference was observed in the physical performance of SLE patients receiving steroids vs that of SLE patients not receiving steroids (See the [Supplementary Data S1](#), available at *Rheumatology* online).

Discussion

This study has investigated the value of US in the assessment of various aspects of muscle involvement (i.e. muscle mass, muscle quality and muscle stiffness) in SLE patients, in comparison with healthy subjects, and their correlations with muscle strength and physical performance. Low muscle strength and reduced physical performance represent two of the three criteria for the diagnosis of sarcopenia according to the EWGSOP and the Asian Working Group for Sarcopenia (ASWG)

Fig. 3 Muscle echogenicity (i.e. semi-quantitative evaluation and grayscale analysis with histograms) and SWE in SLE patients and healthy subjects



(a, b) An US transverse scan of the rectus femoris and vastus intermedius muscles shows different grades of echogenicity in an SLE patient (a) and in a healthy subject (b). The patient with SLE was given a score = 3 (i.e. increased muscle echogenicity in more than two-thirds of muscle tissue), while the healthy subject was given a score = 0 (i.e. normal hypoechoic muscle) according to the modified version of the scale by Heckmatt et al. for the visual semi-quantitative assessment of muscle echogenicity (see Fig. 1 for reference). The region of interest (ROI) for grayscale image analysis is included within the small squares and lines. (c, d) US longitudinal scan of the rectus femoris and vastus intermedius muscles using point shear-wave elastography (SWE). Note the reduced SWE values in the patient with SLE (1.4 m/s, IQR 0.0, Fig. 3c) in comparison with the healthy subject (1.8 m/s, IQR 0.1, Fig. 3d). These measurements were obtained in the 'upper lateral' quadrant of the rectus femoris muscle. The ROI for SWE measurement is defined by the rectangular area. V = velocity; Rel: reliability; IQR/M: interquartile range/median; rf: rectus femoris muscle; vi: vastus intermedius muscle.

[14, 33]. Low muscle strength has also been shown to represent a potential indicator of physical disability in SLE patients [34], and it has been associated with a wide range of poor health outcomes, including cardiovascular events and premature mortality [35]. The results of the current study suggest that the US assessment of muscle echogenicity, a reliable surrogate of muscle quality [36], and/or muscle stiffness, could discriminate between SLE patients and healthy subjects and may improve the early identification of SLE patients with reduced muscle strength and physical performance.

Indeed, no significant difference in muscle mass (i.e. the traditional reference method for US muscle assessment in patients with or at risk of sarcopenia [37]) was observed between SLE patients and healthy subjects. Conversely, increased muscle echogenicity (evaluated semi-quantitatively and by grayscale analysis with histograms), as well as reduced SWE values, were found in SLE patients in comparison with healthy subjects. These findings have various possible interpretations, including the relatively young mean age of the SLE patients

(45.6 years), which is by far younger than that of populations commonly included in studies evaluating sarcopenia. It is known that reduction in muscle mass is a process strongly associated with advanced age, and that it particularly increases after 65 years of age [38]. Interestingly, in the only study evaluating US muscle changes in patients with SLE [22], Kaya *et al.* showed an increase in muscle thickness in the vastus lateralis muscle in SLE patients in comparison with healthy controls, while no difference was observed in the thickness of the gastrocnemius muscle. Another possible interpretation could be that the included SLE patients had relatively well-preserved muscle strength. Although the SLE patients had a reduced hand grip strength in comparison with their healthy subject counterparts, this difference did not reach statistical significance, with only one SLE patient fulfilling the criteria of low muscle strength according to the EWGSOP [14]. Interestingly, studies in healthy young adults have demonstrated that changes in muscle quality may precede changes in muscle size, and the former may significantly impact on the muscle

TABLE 3 Correlation between the different US modalities of muscle assessment (i.e. muscle mass measurement, muscle echogenicity, SWE) in SLE patients and healthy subjects

			Visual semi-quantitative scale	Grayscale analysis with histograms	SWE
RIGHT	Muscle thickness	<i>Rho</i>	-0.12	-0.03	0.06
		<i>P</i>	0.43	0.84	0.68
	Visual semi-quantitative scale	<i>Rho</i>	-	0.65	-0.67
		<i>P</i>	-	<0.01	<0.01
	Grayscale analysis with histograms	<i>Rho</i>	-	-	-0.47
		<i>P</i>	-	-	<0.01
LEFT	Muscle thickness	<i>Rho</i>	-0.08	0.04	0.05
		<i>P</i>	0.60	0.77	0.75
	Visual semi-quantitative scale	<i>Rho</i>	-	0.66	-0.64
		<i>P</i>	-	<0.01	<0.01
	Grayscale analysis with histograms	<i>Rho</i>	-	-	-0.48
		<i>P</i>	-	-	<0.01
BILATERAL	Muscle thickness	<i>Rho</i>	-0.07	0.01	0.02
		<i>P</i>	0.65	0.94	0.92
	Visual semi-quantitative scale	<i>Rho</i>	-	0.71	-0.70
		<i>P</i>	-	<0.01	<0.01
	Grayscale analysis with histograms	<i>Rho</i>	-	-	-0.55
		<i>P</i>	-	-	<0.01

Bold font indicates a significant result. SWE: shear-wave elastography.

function and strength independently of any reduction in muscle mass [39, 40]. This might explain the observation of changes in muscle quality (i.e. increased muscle echogenicity), notwithstanding preserved muscle mass, associated with reduced physical performance (i.e. reduced grip strength and SPPB) in SLE patients and healthy subjects in the current study.

The healthy controls included in our study were all staff members of the hospital, and therefore active people with the ability to work. Although the level of physical activity did not differ between the SLE patients and the healthy subjects (see Table 1), whether the results obtained in the current study would be confirmed in a more sedentary population of healthy controls will need to be further investigated. Similarly, fatigue (a very common clinical manifestation in SLE, with a recognized potential impact on SLE patients' muscle strength and physical performance) [41], as well as arthralgia, should be regarded as potential confounders for the participants' grip strength test and SPPB.

In the current study, we have proposed a visual semi-quantitative scale for the measurement of muscle echogenicity, which is a modified version of the Heckmatt scale [29]. Whereas the Heckmatt scale measures the degree of muscle echointensity (i.e. normal, increased or markedly increased echogenicity), this modified scale grades echointensity abnormalities based on extent of muscle involved (i.e. less than a third, between one-third and two-thirds, or more than two-thirds of the muscle area). The measurement of muscle echogenicity based on the area of muscle involved as opposed to the degree of the echointensity change may present some pitfalls. For example, in patients with muscle atrophy, loss

of contractile muscle tissue can lead to crowding of connective tissue and a seeming increase in echointensity. Therefore, further studies are needed to evaluate the applicability, validity and reliability of the modified semi-quantitative scale developed by the current authors.

The present results also highlight the promising value of SWE, a relatively new US technique that has demonstrated the ability to measure the stiffness of muscle tissue. Recent studies have demonstrated that SWE was able to detect abnormally reduced thigh stiffness in elderly people, as well as in patients with idiopathic inflammatory myositis [42], although this observation was not corroborated by other studies in patients with neuromuscular disorders or RA [43]. In the present study, SWE was able to discriminate the level of muscle stiffness in SLE patients from that in healthy subjects, with the former group showing significantly reduced SWE values compared with the latter. Interestingly, SWE was inversely associated with muscle echogenicity, both when evaluated by a visual semi-quantitative scale or by grayscale analysis with histograms (Table 3), thus suggesting a possible relationship between decreased muscle quality and increased muscle stiffness.

All proposed definitions for sarcopenia include the measurement of muscle mass. Indeed, a low muscle mass represents the *condicio sine qua non* for defining sarcopenia according to the EWGSOP and ASWG criteria [14, 33]. The current results suggest that US assessment of muscle echogenicity and stiffness may provide a quick and reliable differentiation between SLE patients with and without clinically relevant muscle involvement. Further studies are needed to evaluate the potential

long-term benefits of lifestyle interventions (e.g. referral to dedicated physical programs, nutritional supplementation) on those patients with muscle involvement.

The current study has some limitations, the first being the relatively low number of SLE patients. Thus, further investigations in larger cohorts are desirable. Second, an external validation reference (e.g. histology or a reference imaging tool for the assessment of muscle involvement, such as MRI) could have provided a more comprehensive understanding of the US findings (e.g. differentiation between subclinical myositis and steroid myopathy, or sarcopenia) and therefore of their relevance in an asymptomatic population. In addition, the measurement of muscle enzymes would have facilitated the detection of subclinical myositis in SLE patients. Interestingly, no significant difference either in the US findings or in physical performance was observed when assessing SLE patients receiving steroids vs SLE patients not receiving steroids—only a tendency for increased muscle echogenicity (evaluated using the visual semi-quantitative scale) with use of steroids that did not reach statistical significance. These findings could be explained by the relatively low dose of prednisone (6.1 mg/day) of the included patients, and/or to the limited number of SLE patients. Third, the decision to adopt a pragmatic US scanning protocol that included only the evaluation of the quadriceps muscle might have led to under- or over-estimating the prevalence of muscle changes in SLE patients. Our aim was to propose a feasible and reproducible US scanning protocol that could be applied to a systemic condition, such as SLE, in which a homogeneous and broad involvement of muscle structures would be expected. The quadriceps muscle was chosen for its high reliability in several US studies [44, 45], and good correlation with reference imaging tools for the evaluation of muscle involvement, such as MRI or CT scan [46, 47], as well as with appendicular lean mass determined by DXA [48]. In addition, the quadriceps muscle represents one of the earliest targets for the development of age-related muscle wasting [49].

Following the EWGSOP and AWGS recommendations [14, 33], we adopted the hand grip test to measure muscle strength, as this test has been demonstrated to be reliable, and to correlate with muscle strength in other body compartments, therefore serving as an accurate surrogate for more complicated assessments of arm and leg strength [50]. The fact that physical performance tests were not performed at the level of the quadriceps muscle (e.g. knee flexion/extension torque) should be regarded as a limitation of the study, as this could have provided additional and more targeted information about the relationship between the US findings and muscle strength and function.

Conclusions

US evaluation of muscle echogenicity and stiffness, but not US muscle mass, can discriminate between SLE patients and healthy subjects. Multimodal US may be

able to play a key role in the early identification of SLE patients with reduced muscle strength and impaired physical performance.

Acknowledgements

A.D.M. largely designed the study, carried out the US examinations, and wrote the manuscript. G.S. contributed to the design of the study and to development of the visual semi-quantitative scale for the assessment of muscle echogenicity. E.C. performed the statistical analysis. R.J.W., C.V.-E., E.F. and W.G. contributed to the analysis and interpretation of the data and the writing of the manuscript. R.D.A. and A.M.R. are the clinicians who collected the patients' clinical information. V.M. performed the grayscale analysis with histograms for muscle echogenicity and contributed to the analysis of the data. F.S. contributed to the design of the study and to the analysis of the data. S.F. was a research assistant in the study and supervised the assessment of the SLE patients' and healthy subjects' physical performance. All co-authors contributed to critical revision of the manuscript and approved the final version for publication.

Funding: No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

Disclosure statement: R.J.W. has received honoraria from Abbvie, Novartis and GE for US-related educational activities. E.F. has received speaking fees from AbbVie, Amgen, BMS, Janssen, Lilly, Novartis, Roche, Pfizer and UCB, outside the submitted work. W.G. has received speaking fees from Celltrion and Pfizer, outside the submitted work. All of the other authors have declared no conflicts of interest.

Data availability statement

The data underlying this article will be shared upon reasonable request to the corresponding author.

Supplementary data

Supplementary data are available at *Rheumatology* online.

References

- 1 Zoma A. Musculoskeletal involvement in systemic lupus erythematosus. *Lupus* 2004;13:851–3.
- 2 Navarra SV, Torralba TP. The musculoskeletal system and bone metabolism. In: DC Wallace, BH Han, eds. *Dubois' lupus erythematosus and related syndromes*. 9th edn. Philadelphia, USA: Elsevier Ltd, 2018: 407–17.
- 3 Di Matteo A, Smerilli G, Cipolletta E *et al.* Imaging of joint and soft tissue involvement in systemic lupus erythematosus. *Curr Rheumatol Rep* 2021;16:73.

- 4 Di Matteo A, De Angelis R, Cipolletta E *et al.* Systemic lupus erythematosus arthropathy: the sonographic perspective. *Lupus* 2018;27:794–801.
- 5 Di Matteo A, Satulu I, Di Carlo M *et al.* Enteseal involvement in systemic lupus erythematosus: are we missing something? *Lupus* 2017;26:320–8.
- 6 Wong PC, Lee G, Delle Sedie A *et al.* Musculoskeletal ultrasound in systemic lupus erythematosus: systematic literature review by the lupus task force of the OMERACT ultrasound working group. *J Rheumatol* 2019;46:1379–87.
- 7 Cotton T, Niaki OZ, Zheng B *et al.* Myositis in systemic lupus erythematosus. *Lupus* 2021;30:615–9.
- 8 Guis S, Mattéi JP, Lioté F. Drug-induced and toxic myopathies. *Best Pract Res Clin Rheumatol* 2003;17: 877–907.
- 9 Dall’Era M, Wofsy D. Clinical features of systemic lupus erythematosus. In: GS Firestein, RC Budd, SE Gabriel *et al.*, eds. *Firestein & Kelley’s textbook of rheumatology*. Volume II. 11th edn. Philadelphia, USA: Elsevier, 2020: 1413–36.
- 10 Lim KL, Abdul-Wahab R, Lowe J *et al.* Muscle biopsy abnormalities in systemic lupus erythematosus: correlation with clinical and laboratory parameters. *Ann Rheum Dis* 1994;53:178–82.
- 11 Minetto MA, D’Angelo V, Arvat E *et al.* Diagnostic work-up in steroid myopathy. *Endocrine* 2018;60:219–23.
- 12 Gupta S, Dhillon RJS, Hasni S. Sarcopenia: a rheumatic disease? *Rheum Dis Clin North Am* 2018;44: 393–404.
- 13 Barone M, Viggiani MT, Anelli MG *et al.* Sarcopenia in patients with rheumatic diseases: prevalence and associated risk factors. *J Clin Med* 2018;7:504.
- 14 Cruz-Jentoft AJ, Bahat G, Bauer J, Writing Group for the European Working Group on Sarcopenia in Older People 2 (EWGSOP2), and the Extended Group for EWGSOP2 *et al.* Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing* 2019;48:16–31.
- 15 Walston JD. Sarcopenia in older adults. *Curr Opin Rheumatol* 2012;24:623–7.
- 16 Cruz-Jentoft AJ, Romero-Yuste S, Chamizo Carmona E *et al.* Sarcopenia, immune-mediated rheumatic diseases, and nutritional interventions. *Aging Clin Exp Res* 2021; 33:2929–39.
- 17 Albano D, Messina C, Vitale J *et al.* Imaging of sarcopenia: old evidence and new insights. *Eur Radiol* 2020;30:2199–208.
- 18 Sergi G, Trevisan C, Veronese N *et al.* Imaging of sarcopenia. *Eur J Radiol* 2016;85:1519–24.
- 19 Albayda J, van Alfen N. Diagnostic value of muscle ultrasound for myopathies and myositis. *Curr Rheumatol Rep* 2020;22:82.
- 20 Yoshida T, Kumon Y, Takamatsu N *et al.* Ultrasound assessment of sarcopenia in patients with rheumatoid arthritis. *Mod Rheumatol* 2021; Advance Access published 13 September 2021, doi: org/10.1093/mr/roab049
- 21 Farrow M, Biglands J, Alfuraih AM *et al.* Novel muscle imaging in inflammatory rheumatic diseases—a focus on ultrasound shear wave elastography and quantitative MRI. *Front Med (Lausanne)* 2020;7:434.
- 22 Kaya A, Kara M, Tiftik T *et al.* Ultrasonographic evaluation of the muscle architecture in patients with systemic lupus erythematosus. *Clin Rheumatol* 2013;32: 1155–60.
- 23 Petri M, Orbai AM, Alarcón GS *et al.* Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheum* 2012;64:2677–86.
- 24 Gladman DD, Ibanex D, Urowitx MB. Systemic lupus erythematosus disease activity index 2000. *J Rheumatol* 2002;29:28891.
- 25 Legge A, Kirkland S, Rockwood K *et al.* Construction of a frailty index as a novel health measure in systemic lupus erythematosus. *J Rheumatol* 2020;47:72–81.
- 26 Malmstrom TK, Miller DK, Simonsick EM *et al.* SARC-F: a symptom score to predict persons with sarcopenia at risk for poor functional outcomes. *J Cachexia Sarcopenia Muscle* 2016;7:28–3.
- 27 Department of Health. The General Practice Physical Activity Questionnaire (GPPAQ): a screening tool to assess adult physical activity levels, within primary care. 2009. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/192453/GPPAQ_-_guidance.pdf (30 March 2022, date last accessed).
- 28 Smerilli G, Cipolletta E, Tanimura S *et al.* Ultrasound measurement of muscle thickness at the anterior thigh level in rheumatology setting: a reliability study. *Clin Rheumatol* 2021;40:1055–60.
- 29 Heckmatt J, Leeman S, Dubowitz V. Ultrasound imaging in the diagnosis of muscle disease. *J Pediatr* 1982;101: 656–60.
- 30 Salaffi F, Carotti M, Farah S *et al.* Handgrip strength features in rheumatoid arthritis patients assessed using an innovative cylindrical-shaped device: relationships with demographic, anthropometric and clinical variables. *J Med Syst* 2021;45:100.
- 31 Guralnik JM, Simonsick EM, Ferrucci L *et al.* A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol* 1994;49:M85–M94.
- 32 Landis JR, Koch GG. An application of hierarchical kappa-type statistics in the assessment of majority agreement among multiple observers. *Biometric* 1977; 33:363–74.
- 33 Chen LK, Woo J, Assantachai P *et al.* Asian Working Group for Sarcopenia: 2019 Consensus Update on Sarcopenia Diagnosis and Treatment. *J Am Med Dir Assoc* 2020;21:300–7.e2.
- 34 Andrews JS, Trupin L, Schmajuk G *et al.* Muscle strength, muscle mass, and physical disability in women with systemic lupus erythematosus. *Arthritis Care Res (Hoboken)* 2015;67:120–7.
- 35 Celis-Morales CA, Welsh P, Lyall DM *et al.* Associations of grip strength with cardiovascular, respiratory, and cancer outcomes and all cause mortality: prospective cohort study of half a million UK Biobank participants. *BMJ* 2018;8:k1651.

- 36 Stringer HJ, Wilson D. The role of ultrasound as a diagnostic tool for sarcopenia. *J Frailty Aging* 2018;7: 258–61.
- 37 Buckinx F, Landi F, Cesari M *et al.* Pitfalls in the measurement of muscle mass: a need for a reference standard. *J Cachexia Sarcopenia Muscle* 2018;9:269–78.
- 38 Santilli V, Bernetti A, Mangone M *et al.* Clinical definition of sarcopenia. *Clin Cases Miner Bone Metab* 2014;11: 177–80.
- 39 McGregor RA, Cameron-Smith D, Poppitt SD. It is not just muscle mass: a review of muscle quality, composition and metabolism during ageing as determinants of muscle function and mobility in later life. *Longev Healthspan* 2014;3:9.
- 40 Correa-de-Araujo R, Harris-Love MO, Miljkovic I *et al.* The need for standardized assessment of muscle quality in skeletal muscle function deficit and other aging-related muscle dysfunctions: a symposium report. *Front Physiol* 2017;8:87.
- 41 Balsamo S, da Mota LM, de Carvalho JF *et al.* Low dynamic muscle strength and its associations with fatigue, functional performance, and quality of life in premenopausal patients with systemic lupus erythematosus and low disease activity: a case-control study. *BMC Musculoskelet Disord* 2013;14:263.
- 42 Alfuraih AM, Tan AL, O'Connor P *et al.* The effect of ageing on shear wave elastography muscle stiffness in adults. *Aging Clin Exp Res* 2019;31:1755–63.
- 43 Paramalingam S, Morgan K, Becce F *et al.* Conventional ultrasound and elastography as imaging outcome tools in autoimmune myositis: a systematic review by the OMERACT ultrasound group. *Semin Arthritis Rheum* 2021;51:661–76.
- 44 Nijholt W, Scafoglieri A, Jager-Wittenaar H *et al.* The reliability and validity of ultrasound to quantify muscles in older adults: a systematic review. *J Cachexia Sarcopenia Muscle* 2017;8:702–12.
- 45 Weinel LM, Summers MJ, Chapple LA. Ultrasonography to measure quadriceps muscle in critically ill patients: a literature review of reported methodologies. *Anaesth Intensive Care* 2019;47:423–34.
- 46 Mechelli F, Arendt-Nielsen L, Stokes M, Agyapong-Badu S. Validity of ultrasound imaging versus magnetic resonance imaging for measuring anterior thigh muscle, subcutaneous fat, and fascia thickness. *Methods Protoc* 2019 Jul 10;2:58. doi: 10.3390/mps2030058. PMID: 31295936; PMCID: PMC6789827.
- 47 Tourel C, Burnol L, Lanoiselé J *et al.* Reliability of standardized ultrasound measurements of quadriceps muscle thickness in neurological critically ill patients: a comparison to computed tomography measures. *J Rehabil Med* 2020;52:jrm00032.
- 48 Abe T, Patterson KM, Stover CD *et al.* Site-specific thigh muscle loss as an independent phenomenon for age-related muscle loss in middle-aged and older men and women. *Age (Dordr)* 2014;36:9634.
- 49 Miyatani M, Kanehisa H, Azuma K *et al.* Site-related differences in muscle loss with aging. *Int J Sport Health Sci* 2003;1:34–40.
- 50 Lauretani F, Russo CRV, Bandinelli S *et al.* Age-associated changes in skeletal muscles and their effect on mobility: an operational diagnosis of sarcopenia. *J Appl Physiol* (1985) 2003;95:1851–60.