Maturitas 168 (2023) 29–36

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Original article

Fat infiltration and muscle hydration improve after high-intensity resistance training in women with sarcopenia. A randomized clinical trial

Cristina Flor-Rufino [a], Joaquín Barrachina-Igual [b], Pilar Pérez-Ros [c,d,*], Ana Pablos-Monzó [b], Roberto Sanz-Requena [d], Francisco M. Martínez-Arnau [a,d]

[a] Department of Physiotherapy, Universitat de València, Gascó Oliag 5, 46010 Valencia, Spain
[b] Faculty of Physical Activity and Sport Sciences, Universidad Católica de València San Vicente Mártir, Ramiro de Maetzu 14, 46900 Torrent, Valencia, Spain
[c] Department of Nursing, Universitat de València, Menéndez y Pelayo, 19, 46010 Valencia, Spain
[d] ICT Deparment, Florida Universitaria, C/ Rei en Jaume I, n° 2. 46470 CATARROJA (Valencia)

ARTICLE INFO

Keywords:
Sarcopenia
Resistance training
Aged
Ageing
magnetic resonance imaging

ABSTRACT

Background: Resistance training is recommended for preventing sarcopenia, but the benefits for the quality and quantity of muscle mass are uncertain.
Objective: To assess the effects of high-intensity resistance training (HIRT) on clinical and magnetic resonance imaging (MRI) parameters in women with sarcopenia.
Methods: A researcher-blinded randomized clinical trial was conducted. Community-dwelling older women with sarcopenia were randomized to six months of HIRT or a control group (CG). Body composition was assessed with bioimpedance equipment, and participants underwent strength and functional performance tests (short physical performance battery [SPPB] and gait speed). MRI scans of the thigh were taken to quantify muscle mass and quality.
Results: Thirty-eight women completed the study (20 in the HIRT group). Sarcopenia remitted in 50 % of the HIRT group. HIRT elicited a significant group × time interaction effect for muscle mass ($p = 0.027$; $\eta^2 = 0.129$), muscle mass index ($p = 0.023$; $\eta^2 = 0.135$), fat mass ($p = 0.048$; $\eta^2 = 0.103$) and all strength variables ($p < 0.05$; $\eta^2 > 0.120$). Moreover, the HIRT group obtained higher scores on the SPPB (mean difference [MD] 1.2; $p = 0.005$) and the 5 times sit-to-stand test (MD = 0.7; $p = 0.009$). Regarding MRI parameters, infiltrated microscopic fat decreased significantly (HIRT: MD = −0.01; $p < 0.05$), while hydration (T2) decreased in the CG (MD = 3.6 ms; $p = 0.053$) at six months. There were significant between-group differences at six months for water diffusion (HIRT: 1.09×10^{-3} mm^2/s vs CG: 1.26×10^{-3} mm^2/s) and total muscular volume (HIRT: 832.4 L vs CG: 649.2 L).
Conclusions: HIRT led to the remission of sarcopenia in half of the older women, as seen in muscle mass, strength, and functional performance and MRI biomarkers, with significant increases in muscle quality.
Registered in ClinicalTrials.gov: NCT03834558.

1. Introduction

From 2015 to 2050, the proportion of people over 60 will double, and the percentage of dependent elders will quadruple [1]. One of the main consequences of the loss of function is the decline of the locomotor system and particularly the decrease in muscle mass, also called sarcopenia. The European Working Group on Sarcopenia in Older People (EWGSOP) published guidelines for sarcopenia in 2010 [2]. The definition of sarcopenia has evolved and is currently proposed from a two-dimensional perspective, taking into account the loss of both muscle mass and muscle function [3]. Nevertheless, while it is important to preserve lean mass, muscle quality also plays an important role in muscle function and functional performance [4].

International guidelines strongly recommend the prescription of resistance-based training to manage sarcopenia [5], as it can be effective to improve muscle mass [6], muscle strength [7], and physical

* Corresponding author at: Avda Menéndez y Pelayo, 19, 46010 Valencia, Spain.
E-mail addresses: cristina.flor@uv.es (C. Flor-Rufino), joaquin.barrachina@ucv.es (J. Barrachina-Igual), maria.p.perez-ros@uv.es (P. Pérez-Ros), ana.pablos@ucv.es (A. Pablos-Monzó), rsanz@florida-uni.es (R. Sanz-Requena), francisco.m.martinez@uv.es (F.M. Martínez-Arnau).

https://doi.org/10.1016/j.maturitas.2022.09.001
Received 22 June 2022; Received in revised form 25 August 2022; Accepted 3 September 2022
Available online 4 November 2022

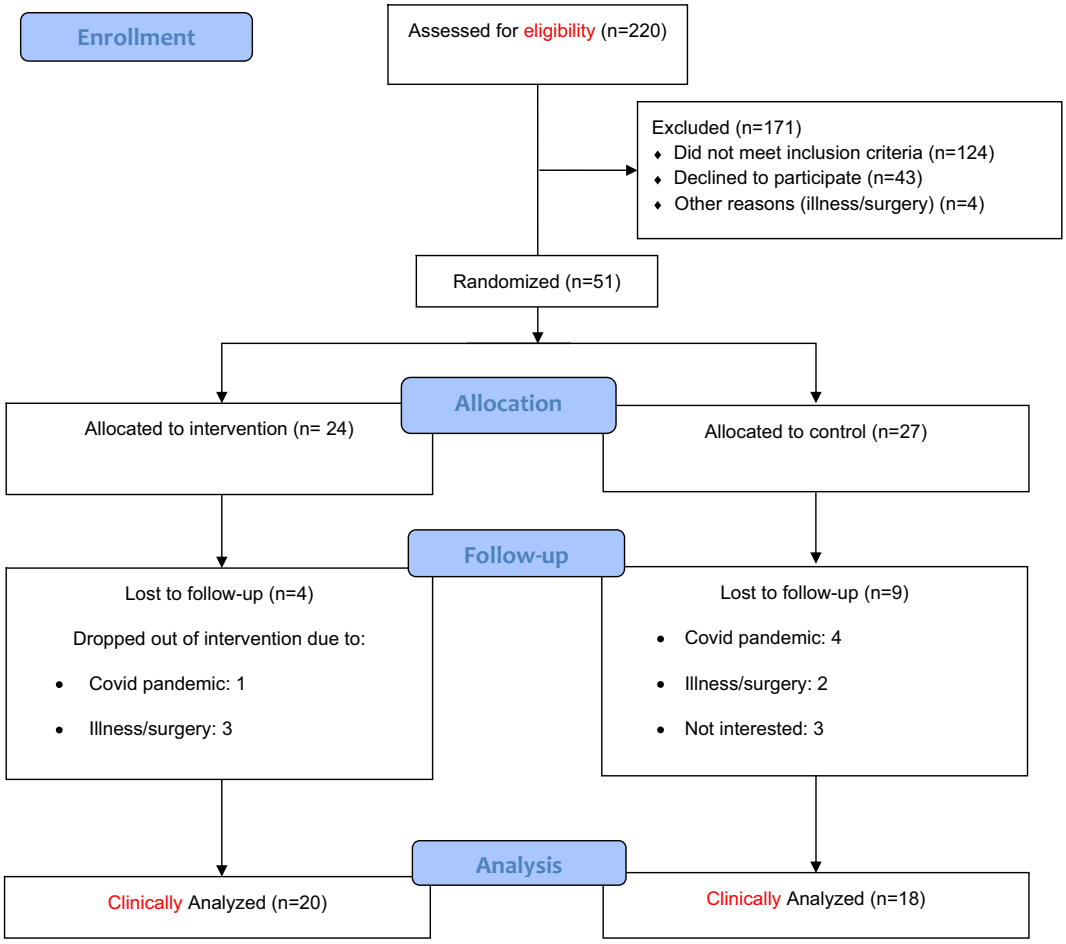

Fig. 1. CONSORT diagram showing participant flow through the trial (clinical variables).

performance [8], even in very old people [9]. The intensity of a training program can be determined from the use of 1 repetition maximum (1RM) [10]. Some analyses have classified high-intensity resistance training (HIRT) as a workout at >70 % 1 RM [10]. Studies show that higher-intensity resistance training is better for improving muscle strength [11], but greater changes in lean body mass were found with higher volumes of work. Nevertheless, newer research suggests that muscle hypertrophy can be equally achieved with different training loads [11] and that working until muscle failure is the most important factor [11–13]. A recent systematic review showed that physical activity improves physical performance and strength in people with sarcopenia, but its effect is inconsistent for muscle mass. Nevertheless, authors highlight the need for more randomized controlled trials (RCTs) to evaluate the isolated effects of physical activity [14].

Diagnosis of sarcopenia is based on clinical criteria, but the certainty of these parameters increases with biological and imaging markers like magnetic resonance imaging (MRI), considered the gold standard. Although there is no protocol with specific MRI biomarkers to characterize patients with sarcopenia, Sanz-Requena et al. has recently proposed a series of MRI-derived imaging parameters [15].

Both the lack of global consensus on the diagnostic criteria for sarcopenia and the methodological heterogeneity of exercise programs applied justify the need for RCTs with quantified programs [14]. At the same time, it is essential to add imaging techniques that elucidate the effect of exercise on muscle quantity and quality, given the absence of longitudinal studies that use this tool in people with sarcopenia. This study aimed to assess the effects of HIRT on EWGSOP-defined sarcopenia, kinanthropometric variables, muscle function, functional performance, and imaging biomarkers.

2. Material and methods

2.1. Study design and participants

We designed a single (researcher)-blinded RCT based on a six-month HIRT intervention in community-dwelling older women with sarcopenia. The study period was October 2018 to March 2020. It was approved by the Research Ethics Committee of the Universitat de València (H1488746567568), which operates in accordance with the principles of the Declaration of Helsinki. The trial was registered with the US National Institutes of Health (ClinicalTrials.gov, NCT03834558).

Inclusion criteria were: women aged 70 or older and diagnosed with sarcopenia according to EWGSOP consensus criteria [2], able to walk independently (with or without technical aids), residing in the community in the health areas under study, and signed informed consent. Exclusion criteria were: life expectancy of less than six months, living in an institution, severe auditory or visual impairment, medical contraindication to performing physical activity, or contraindication for the MRI study (especially carriers of non-compatible pacemakers, neurostimulators, cochlear implants, and intracranial aneurysm clamping), severe psychiatric illness or moderate-to-severe cognitive impairment; refusal to sign informed consent prior to participation.

2.2. Sample size

Estimation of sample size for this investigation was performed using handgrip strength as one of our primary outcome measures. Sample size was estimated combining the normative data and the genuine change in grip strength determined in previous works [16]. These assumptions

Table 1
Baseline participant characteristics.

Variable	Total Mean (SD) (n = 38)	HIRT Mean (SD) (n = 20)	Control Mean (SD) (n = 18)	p value
Age (years)	79.8 (7.4)	79.9 (7.2)	79.6 (7.7)	0.91
Height (m)	1.5 (0.1)	1.5 (0.1)	1.5 (0.1)	0.79
Body weight (kg)	61.5 (9.1)	59.6 (9.6)	63.6 (8.2)	0.19
BMI (kg/m^2)	26.9 (3.7)	26.2 (4.2)	27.7 (2.9)	0.21
Brachial perimeter (cm)	26.9 (2.7)	26.3 (2.6)	27.5 (2.8)	0.17
Calf perimeter (cm)	32.6 (2.4)	32.3 (2.0)	33.0 (2.9)	0.40
Thigh perimeter (cm)	48.4 (4.5)	47.2 (3.8)	49.6 (5.1)	0.098
Charlson Index (points)	5.2 (1.8)	5.4 (2.1)	5.1 (1.5)	0.36
Fat mass (kg)	23.7 (6.3)	22.5 (7.1)	25.0 (5.2)	0.23
Muscle mass (kg)	36.1 (3.7)	35.2 (4.0)	37.1 (3.0)	0.11
Skeletal muscle index (kg/cm^2)	5.7 (0.7)	5.6 (0.8)	5.9 (0.6)	0.57
Handgrip (kg)	18.2 (3.8)	17.8 (3.2)	18.6 (4.4)	0.51
MIC of knee extension (kg)[a]	16.5 (6.2)	17.6 (6.7)	15.2 (5.4)	0.25
Average-MIC of knee extension (kg)[a]	14.9 (5.9)	15.9 (6.5)	13.6 (5.0)	0.26
1RM knee extension (kg)	3.2 (3.4)	3.7 (3.7)	2.8 (3.2)	0.42
1RM leg press (kg)	59.2 (19.3)	58.6 (21.0)	59.9 (17.9)	0.84
Gait speed (m/s)	0.75 (0.21)	0.79 (0.24)	0.71 (0.16)	0.23
Short Physical Performance Battery				
Total (points)	7.8 (2.5)	7.9 (2.7)	7.7 (2.3)	0.83
Balance (points)	2.9 (1.2)	2.7 (1.1)	3.1 (1.2)	0.36
Walk (points)	2.7 (0.9)	2.9 (0.9)	2.4 (0.8)	0.16
5 times sit-to-stand (points)	2.3 (1.4)	2.4 (1.5)	2.22 (1.3)	0.78
Barthel Index (points)	93.6 (8.0)	93.5 (9.5)	93.6 (6.1)	0.57
International Physical Activity Questionnaire-Elderly (metabolic equivalent of task)	868.3 (731.9)	882.1 (830.7)	853 (628.0)	0.97
Mini Nutritional Assessment-Short Form (points)	12.5 (2.0)	11.9 (2.4)	13.1 (1.3)	0.057

Average-MIC: average of maximum isometric contraction; HIRT: high-intensity resistance training; MIC: maximum isometric contraction; SD: standard deviation; 1RM: 1 repetition maximum.

[a] 16 participants were registered in the HIRT group; 2 could not perform the test.

generated a desired sample size of at least 30 participants.

Participants were recruited through social centers for older adults in the city of Valencia (Spain), primary health care centers in the Valencia University Clinical Hospital health department, and the Hospital QuironSalud of Valencia.

We used the sarcopenia criteria established by the EWGSOP [2] to diagnose sarcopenia. The presence of low muscle mass (skeletal muscle index [SMI] < 6.68 kg/m^2) [17] and weakness (handgrip strength < 20 kg) and/or low functional performance (gait speed ≤ 0.8 m/s) [2] is necessary to diagnose sarcopenia (Appendices). After clinically evaluating 220 patients, 51 remained eligible and were evenly allocated to the HIRT intervention or control group (CG) using computer-based randomization.

2.3. Randomization

The 51 participants were assigned an identification number and allocated using computer-based block randomization, through the computer tool XLstats (XL stats. New York: Addinsoft Inc.; 2017) (HIRT n = 27; CG n = 24). A block size of four was established to ensure an equal chance of allocation to each group; allocation ratio 1:1. To guarantee secrecy, the sequence was generated by a statistician and given to the project manager.

2.4. Process

The study took place in the physical performance laboratory of the University of Valencia Physiotherapy School. To obtain data for between- and within-group comparisons, members of the research team who were not involved in implementing the intervention performed two measurements, one week before implementing the program and one week after its completion.

Variables collected were kinanthropometric measures, muscle function, physical performance, and imaging biomarkers. To characterize the sample, we assessed the presence of comorbidities, the level of physical activity, the independence in activities of daily living and nutritional status (Appendices).

2.5. Variables

2.5.1. Kinanthropometric variables

Bioelectrical impedance analyses (BIA) were carried out with a BC-418 MA BIA device (Tanita 2016, America) to measure body weight, muscle mass and fat mass. Height was measured with a stadiometer, and body mass index (BMI) was calculated. Calf and thigh perimeters were measured with a metric tape. SMI was calculated as muscle mass/height (kg/m^2) (Appendices).

2.5.2. Muscular function

Maximum isometric contractions (MIC) of the dominant leg were assessed using a hand-held dynamometer (model 01165, LaFayette, USA) [3]. We followed the protocol described by Francis et al. [15]. Participants performed three MICs (kg) of knee extensors for 3 s, with 2-min rest periods between them, and we recorded the best (MIC) and mean values (average-MIC) [15]. Leg extension and seated leg press gym machines (F&H Fitness Equipment, Spain) were used to assess maximum dynamic muscle strength on the knees. Given the characteristics of the sample, we decided to calculate the predicted maximum strength using a submaximal maneuver. The Jamar Hydraulic Hand Dynamometer 5030J1 (Loughborough, UK) was used to measure dominant handgrip. We recorded the maximum value out of three assessments (Appendices).

2.5.3. Functional performance

Gait speed and the short physical performance battery (SPPB) were evaluated (Appendices).

2.5.4. Imaging biomarkers obtained from MRI sequences

MRI studies were performed within a week from the clinical and functional assessments, in the Radiology Service of the Hospital Quironsalud of Valencia, using a 3 Tesla unit (Philips Achieva, Philips Healthcare, Best, the Netherlands). We followed the image analysis protocol which has been published recently [15]. The study focused on the mid-thigh, and the following imaging biomarkers were used: water apparent diffusion coefficient (ADC), water interstitial diffusion coefficient (D), tissue hydration as transversal relaxation time (T2), proton density fat fraction (PDFF), fat/muscle/bone volumes, and macroscopic fatty infiltration.

2.6. High-intensity resistance training (HIRT)

The HIRT intervention consisted of two weekly 65 min sessions for six months, with a minimum recovery time of 72 h. Finally, participants in the HIRT group took part in up to 39 sessions (due to the university's vacation period). Each session consisted of three parts, starting with a 10-minute warm up, including joint mobility and postural control exercises. This was followed by a 45-min HIRT circuit, with six exercises to strengthen different muscle groups (two on the upper extremities, two on the trunk and two on the lower extremities). The present study focused only on the two lower extremity exercises (leg press and knee extension). Participants did three series of 10–15 repetitions until

Table 2
Results of the intra-group (time) analysis and time × group (interaction) comparative analysis for the clinic variables.

Variable			Baseline Mean (SD)	Postintervention Mean (SD)	Within-group Mean difference (95 % CI)	Time × group (between-groups)		
						F	p value	η^2
SMI (kg/m^2)		Control (n = 18)	5.85 (0.58)	5.79 (0.76)	−0.06 (−0.33, 0.22)	5.617	0.023*	0.135
		HIRT (n = 20)	5.63 (0.79)	6.02 (0.68)	0.39 (0.13, 0.65)**			
Muscle mass (kg)		Control (n = 18)	37.12 (2.97)	36.43 (4.13)	−0.69 (−1.82, 0.44)	5.331	0.027*	0.129
		HIRT (n = 20)	35.20 (4.04)	36.30 (4.07)	1.11 (0.02, 2.19)*			
Fat mass (kg)		Control (n = 18)	25.04 (5.20)	25.89 (6.61)	0.85 (−0.65, 2.35)	4.112	0.048*	0.103
		HIRT (n = 20)	22.53 (7.09)	21.29 (6.40)	−1.25 (−2.69, 0.20)			
Body weight (kg)		Control (n = 18)	63.55 (8.23)	63.44 (9.07)	−0.11 (−1.08, 0.86)	0.001	0.97	<0.001
		HIRT (n = 20)	59.63 (9.60)	59.50 (9.74)	−0.14 (−1.05, 0.78)			
BMI (kg/m^2)		Control (n = 18)	27.69 (2.89)	27.52 (3.32)	−0.17 (−0.54, 0.20)	<0.001	0.99	<0.001
		HIRT (n = 20)	26.18 (4.24)	26.02 (4.32)	−0.16 (−0.51, 0.19)			
Handgrip (kg)		Control (n = 18)	18.64 (4.41)	17.56 (5.61)	−1.08 (−2.88, 0.71)	5.256	0.028*	0.127
		HIRT (n = 20)	17.80 (3.24)	19.55 (3.98)	1.75 (0.03, 3.48)*			
Maximum isometric contraction knee extension (kg)[a]		Control (n = 19)	15.47 (5.49)	17.19 (7.89)	1.72 (−1.19, 4.63)	4.434	0.043*	0.122
		HIRT (n = 15)	17.79 (6.80)	23.53 (7.43)	5.74 (3.16, 8.32)**			
Average- maximum isometric contraction knee extension (kg)[a]		Control (n = 19)	13.89 (5.10)	15.80 (7.24)	1.91 (−0.80, 4.61)	5.214	0.029*	0.140
		HIRT (n = 15)	16.15 (6.59)	22.11 (7.31)	5.96 (3.56, 8.36)**			
1 repetition maximum knee extension (kg)		Control (n = 18)	2.75 (3.17)	2.59 (2.99)	−0.16 (−2.03, 1.70)	40.912	<0.001**	0.532
		HIRT (n = 20)	3.68 (3.69)	11.32 (6.52)	7.65 (5.94, 9.35)**			
1 repetition maximum leg press (kg)		Control (n = 18)	59.87 (17.88)	58.13 (21.22)	−1.74 (−10.82, 7.34)	17.301	<0.001**	0.325
		HIRT (n = 20)	58.61 (21.02)	82.54 (19.62)	23.94 (15.32, 32.55)**			
Gait speed (m/s)		Control (n = 18)	0.71 (0.16)	0.76 (0.24)	0.04 (−0.03, 0.12)	0.030	0.864	0.001
		HIRT (n = 20)	0.79 (0.24)	0.85 (0.22)	0.05 (−0.02, 0.13)			
SPPB (points)	Total	Control (n = 18)	7.72 (2.32)	8.17 (2.87)	0.44 (−0.42:1.31)	1.655	0.206	0.044
		HIRT (n = 20)	7.57 (3.06)	8.67 (3.51)	1.20 (0.38, 2.02)**			
	Balance	Control (n = 18)	3.06 (1.21)	3.17 (1.20)	0.11 (−0.56, 0.78)	0.403	0.529	0.011
		HIRT (n = 20)	2.70 (1.13)	3.10 (1.29)	0.40 (−0.24, 1.04)			
	Walk	Control (n = 18)	2.44 (0.78)	2.5 (0.99)	0.06 (−0.21, 0.21)	0.265	0.610	0.007
		HIRT (n = 20)	2.85 (0.93)	3.00 (0.86)	0.15 (−0.11, 0.41)			
	5STS	Control (n = 18)	2.22 (1.26)	2.44 (1.42)	0.22 (−0.28, 0.72)	1.574	0.218	0.042
		HIRT (n = 20)	2.35 (1.46)	3.00 (1.56)	0.65 (0.17, 1.13)**			

BMI: body mass index; CI: confidence interval; HIRT: high-intensity resistance training; F: two-way ANOVA (repeated measures); SD: standard deviation; SMI: skeletal muscle index; SPPB: short physical performance battery; 5STS: five times sit-to-stand; η^2 = eta squared (effect size); thresholds of η^2 >0.01 considered small, >0.059 moderate, and > 0.138 large.

* $p < 0.05$.

** $p < 0.01$.

[a] A total of 16 participants were allocated to the HIRT group; 2 participants could not perform the test.

momentary failure [11–13]. After a period of individualized progression in training, the load was set to at least 70 % of 1RM. Finally, during a 10-min cool down phase, participants did self-massage for myofascial release and stretching exercises (Appendices).

Two senior researchers (a graduate in physical and sports educations and a physical therapist) supervised and managed the interventions, applying corrective measures when necessary to correct posture, breathing, and technique to ensure proper execution and avoid injuries. Attendance to the sessions was recorded daily, and adherence was categorized as high (>65 % of sessions), moderate (34–65 %), or low (<34 %).

The CG did not receive any specific intervention for sarcopenia. Their participation in the trial was limited to telephone follow-ups to assess their general health status.

2.7. Statistical analyses

All analyses were performed using IBM SPSS Statistics v22.0 (SPSS Inc., Chicago, IL, USA) software for Windows. Descriptive statistics were conducted for all variables at baseline, with quantitative data presented as means and standard deviation (SD) and qualitative data as absolute and relative frequencies. Moreover, groups were compared at baseline using the student *t*-test for quantitative variables and contingency tables and the chi-squared test for qualitative variables and sarcopenia status. We report the p value of the asymptotic significance test.

Quantitative variables were analyzed in a two-way mixed-effect (between-within) ANOVA, including 2 (HIRT and CG) × 2 (time: pre-test, post-test) to assess the group × time interaction with repeated measures on the last factor using 95 % confidence intervals (CIs). Statistical significance was set at $p < 0.05$ for all tests. Effect sizes (eta squared, η^2) for ANOVA were also calculated, with thresholds of >0.01 considered small, > 0.059, considered moderate and >0.138 considered large (Appendices). Bonferroni adjustments and post-hoc pairwise comparison were used.

3. Results

Fifty-one older women with sarcopenia were randomized (HIRT n = 24; CG n = 27; mean age 79.8 years SD 7.4), and 38 (74.5 %) fully completed the postintervention assessment (HIRT n = 20; CG = 18; Fig. 1). Of the 51 randomized people, 30 accepted the MRI analysis at the beginning and the end of the study (HIRT n = 14; CG = 16). Eight participants dropped out (HIRT n = 3; CG n = 5) due to the COVID-19 pandemic (HIRT n = 3; CG n = 3), one died (CG n = 1), and one was excluded because of an error in the imaging process (CG n = 1), so 22 participants were finally analyzed by MRI after intervention (HIRT n = 11; CG n = 11). Characteristics of the sample are presented in Table 1. Adherence was high in 75 % of participants, moderate in 20 %, and low in 5 %. Three cases of muscle discomfort attributed to intervention were observed after the first two weeks of HIRT. In all cases, the training load was adapted in the following sessions, returning to normality.

3.1. Kinanthropometric variables

A significant group×time interaction effect was observed for body composition variables: SMI, muscle mass and fat mass measured by BIA, with a moderate effect size. The HIRT also showed an increase in muscle mass (mean difference [MD] 1.1 kg; $p < 0.05$) and SMI (MD 0.4 kg/m^2;

Table 3
Results of the intra-group (time) analysis and time × group (interaction) comparative analysis for the MRI variables.

Variable		Baseline Mean (SD)	Postintervention Mean (SD)	Within-group Mean difference (95 % CI)	Time × group (between-groups)		
					F	p value	η^2
Apparent diffusion coefficient (10^{-3} mm^2/s)	Control (n = 11)	1.11 (0.05)	1.04 (0.10)	-7.17×10^{-5} (0.10×10^{-3}, -3.79×10^{-6})	1.381	0.25	0.065
	HIRT (n = 11)	0.99 (0.12)	0.98 (0.11)	-1.04×10^{-5} (-8.73×10^{-5}, 6.65×10^{-5})			
Diffusion coefficient (10^{-3} mm^2/s)	Control (n = 11)	1.16 (0.16)	1.26 (0.22)	0.10×10^{-3} (-1.08×10^{-5}, 0.10×10^{-5})	1.822	0.19	0.083
	HIRT (n = 11)	1.09 (0.09)	1.09 (0.13)	-8.71×10^{-7} (0.10×10^{-9}, 0.10×10^{-7})			
T2* (relaxation time, ms)	Control (n = 11)	37.72 (3.19)	34.13 (6.26)	−3.59 (−7.17, −0.01)*	2.283	0.15	0.102
	HIRT (n = 11)	37.29 (2.61)	37.43 (2.04)	0.14 (−3.50, 3.77)			
Absolute fat volume (L)	Control (n = 11)	994.07 (409.57)	1063.74 (446.66)	69.67 (−19.03, 158.4)	1.171	0.29	0.055
	HIRT (n = 11)	1401.49 (532.58)	1406.08 (625.32)	4.59 (−84.1, 93.3)			
Proton density fat fraction (no units)	Control (n = 11)	0.20 (0.02)	0.20 (0.02)	0.10×10^{-3} (-0.01, 0.10×10^{-5})	1.918	0.18	0.088
	HIRT (n = 11)	0.21 (0.02)	0.20 (0.02)	-0.01 (-0.10×10^{-3}, -0.10×10^{-4})*			
Macroscopic fatty infiltration (no units)	Control (n = 11)	0.33 (0.11)	0.32 (0.13)	−0.02 (−0.08, 0.04)	0.019	0.89	0.001
	HIRT (n = 11)	0.29 (0.09)	0.27 (0.09)	−0.01 (−0.07, 0.05)**			
Absolute muscle volume (L)	Control (n = 11)	657.00 (278.90)	649.18 (179.63)	−7.82 (−90.76, 75.12)	0.011	0.92	0.001
	HIRT (n = 11)	845.91 (201.49)	832.36 (164.40)	−13.55 (−92.46, 65.37)			
Muscle/fat ratio (no units)	Control (n = 11)	0.75 (0.32)	0.74 (0.39)	−0.01 (−0.09, 0.08)	0.246	0.63	0.012
	HIRT (n = 11)	0.67 (0.27)	0.69 (0.31)	0.02 (−0.06, 0.10)			
Muscle/bone ratio (no units)	Control (n = 11)	12.99 (3.49)	13.08 (3.36)	0.08 (−1.42, 1.59)	0.359	0.56	0.018
	HIRT (n = 11)	13.64 (3.85)	14.28 (4.10)	0.64 (−0.73, 2.01)			

CI: confident interval; HIRT: high-intensity resistance training; F: two-way ANOVA (repeated measures); SD: standard deviation; η^2 = eta squared (effect size); thresholds of η^2 >0.01 considered small, >0.059 moderate, and > 0.138 large.
* $p < 0.05$.
** $p < 0.01$.

$p < 0.001$) in within-group analyses (Table 2).

3.2. Muscular function and physical performance variables

There was a significant interaction effect in strength variables: handgrip, MIC and average-MIC for knee extension, and leg press and knee extension 1RM variables. The effect size was large for average-MIC, 1RM leg press and 1RM knee extension, and moderate for handgrip and MIC. We found significant statistical increases in the HIRT group for total SPPB (MD 1.2 points, 95 % CI 0.38, 2.02; t(37) = 2.97, p = 0.005, r = 0.44) as well as for the 5STS test (MD 0.7 points, 95 % CI 0.17, 1.13; t(37) = 2.77; p = 0.009; r = 0.41), both with moderate effect size (Table 2).

3.3. Imaging biomarkers

Results of the mixed ANOVA of MRI biomarkers are shown in Table 3. At study end, we found a significant decline in PDFF in the HIRT group (MD −0.01, 95 % CI −0.02, −0.002; t(21) = −2.5; p = 0.021; r = 0.48) with a moderate-to-large effect size, while the CG showed no change. We also observed a tendency (p = 0.053) towards a decrease in muscular hydration level of T2* in the CG at six months. We observed significant differences in post-hoc analysis of baseline ADC variables between groups (MD 1.1×10^{-3}, p = 0.003). Furthermore, we obtained significant between-group differences in post-intervention tests for D (MD 1.1×10^{-3}, p = 0.039) and for absolute muscular volume (MD 183.2 L p = 0.021) (Fig. 2). No significant effects were observed in the group × time interaction analysis for any MRI variables.

3.4. Improvement of sarcopenia status

At the beginning of the study, 100 % of the sample (HIRT n = 20; CG n = 18) presented sarcopenia. After six months of HIRT, 50 % (n = 10) of the intervention group had experienced remission of their sarcopenia, while severity decreased in the remaining 45 % (n = 9). In the CG, 27.8 % (n = 5) of the participants had no sarcopenia at six-month follow-up, and a similar proportion had severe sarcopenia (n = 6). There were no significant differences between groups in sarcopenia status ($\eta^2 = 1.96$; p = 0.162) or sarcopenia severity ($\eta^2 = 0.33$; p = 0.564) postintervention.

4. Discussion

Diverse studies have analyzed the effects of resistance training programs in older people with sarcopenia [18–20], but ours is the first to study the influence of HIRT on MRI biomarkers in this population. Six months of HIRT led to an increase in muscular mass, a decrease in body fat mass assessed by BIA, and enhanced muscular strength and performance in the upper and lower limbs. Moreover, at within-group level, we observed improvements in muscular hydration and microscopic fat at midthigh in MRI analysis.

Of the women receiving HIRT, 50 % experienced remission of their sarcopenia, while its severity diminished in almost all of the rest. These results are better than those achieved using lower-intensity resistance training programs of a similar duration [19,20]. In fact, Hassan et al. [20] reported an increase in the prevalence of sarcopenia in institutionalized old people after resistance training, generating more dependence after the intervention.

Regarding body composition variables, we reported changes in muscle mass and fat mass of greater magnitude than in previous studies

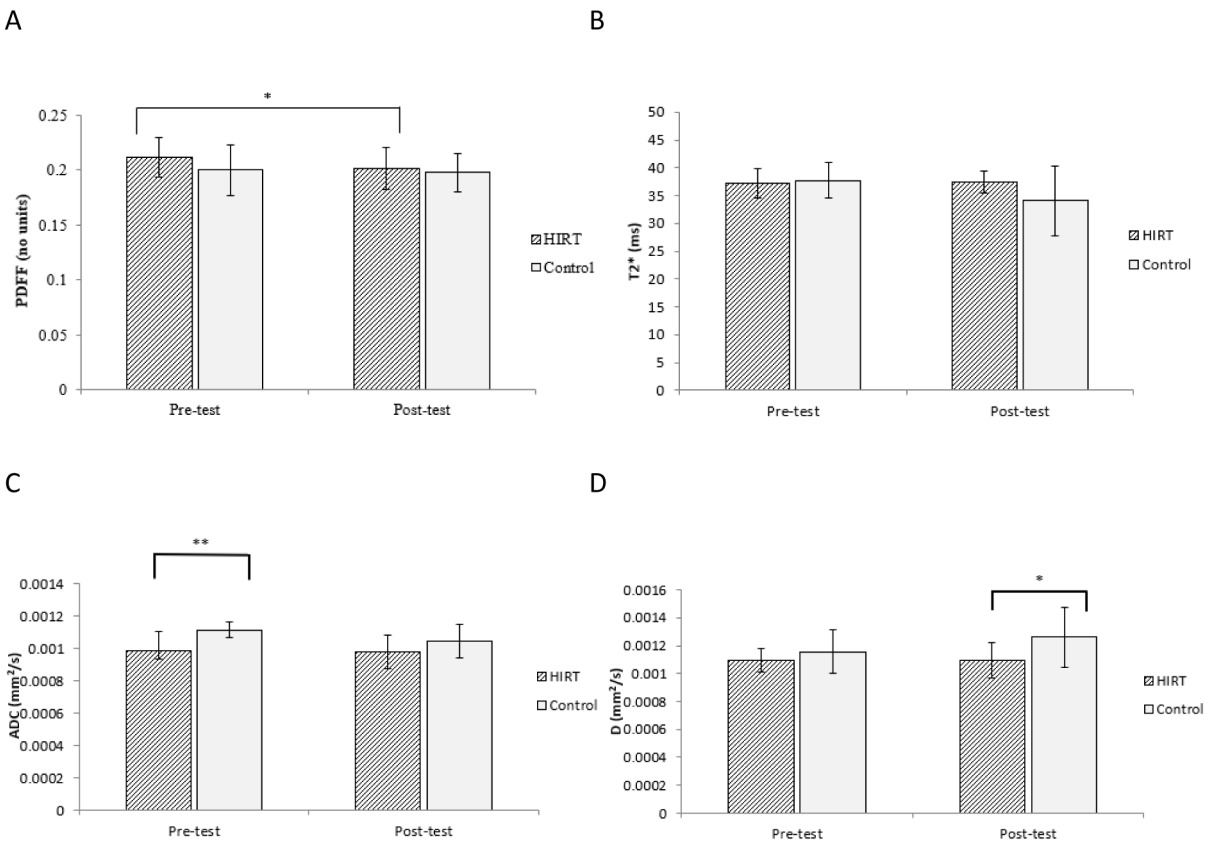

Fig. 2. Results of mixed ANOVA (pre-post differences within-group and between-group differences) for proton density fat fraction (PDFF, A), relaxation time (T2*, B), apparent diffusion coefficient (ADC, C) and diffusion (D) variables (D). Values expressed as mean and SD. Statistical significance was set at *p < 0.05 and **p < 0.01.

of both high [18] and moderate intensity [19,20].

Our results show an improvement in all strength variables after HIRT, compared to no change in the CG. Strength increased similar to other studies [18–21] in terms of both leg and hand isometrics and isotonics, reflecting the balance between intensity and duration of the intervention [14]. We reported greater 1RM values, so HIRT produces improvements in neural factors implicated in force production [7], which results in significantly increased physical ability (SPPB and 5STS) [14], which is consistent with other physical activity interventions in older people [22] and people with sarcopenia [23,24]. Although the change reported in gait speed was not significant, an increase of 0.06 m/s could be considered a small but clinically significant change [25]. Achieving more pronounced improvement could require specific exercises that focus on walking ability [14] or perhaps other kinds of tests that assess walking ability at longer distances [26].

The effects of HIRT on clinical variables were confirmed by MRI parameters. The most common parameter to assess the efficacy of an intervention is muscular volume, although its responsiveness to change depends on exercise type and the specific analysis of muscular volume. In our study, both groups reported a decrease in total muscular volume and an increase in total fat volume, which was more notable in CG. These results can be explained by the behavior of ratio parameters. The HIRT group showed an increase in the muscle/fat ratio, indicative of less loss of muscle than of fat, as opposed to CG. Considering the constant nature of bone volume [21], the improvement in muscle is corroborated in the HIRT group by an increase in the muscle/bone ratio. Therefore, although there was an apparent decrease in total muscle volume, which could be attributable to the loss of BMI, the ratios are positive with respect to fat and bone, a finding that is consistent with Grimm et al.'s study in young people [27].

Physical exercise tends to increase the cross-sectional area of the thigh or quadriceps heterogeneously [14,21], due to the type of exercise and methodological differences in the analysis of inter- and intramuscular fat mass, making it necessary to assess muscle quality in older adults with sarcopenia [4].

Fat mass infiltration and muscular hydration were among the muscle quality parameters analyzed. Previous studies have reported a positive relationship between age and muscle fat infiltration [28]. These fat deposits in the skeletal muscle affect neuromuscular activation and contribute to sarcopenia. We evaluated microscopic fat infiltration using the PDFF variable. Participants receiving HIRT showed a significant decrease in PDFF, in line with previous studies [29], which may contribute to improving or maintaining independence in older people.

Regarding muscular hydration, we studied T2*, ADC and D parameters, which refer to the volume of muscle hydration and the microscopic mobility capacity of intratissue water, respectively. At six months, D values increased in the CG, which could be related with less movements of intratissue water due to the disestablishment (breakdown) of the muscle fibers and the presence of greater fat infiltration [30]. The HIRT group showed no changes in D. On the other hand, we observed a reduction of T2* in the CG at study end, an effect that may be associated with the presence of a greater extracellular space in atrophied muscles [30] and a greater presence of fat at intra and extra muscular level [15], related to muscular deterioration processes. In the CG, this was accompanied by lower lean mass in the different variables analyzed. Another hypothesis would indicate that the age-related decrease in T2* could be associated with an increase in extracellular water/total water rate [30], since the intracellular water value, which reflects muscle cell mass, significantly decreases with age, while extracellular water remains constant [30]. Both of these theories would reinforce our results, where the CG presented lower T2* values and higher levels of fat mass after six months, and they are concordant with the hypothesis postulated by

Sanz-Requena et al., who speculated that people with lower fat mass show higher values of T2* and ADC because metabolic muscle activity is more preserved and muscle quality is higher [15]. All this would relate to a worse hydration level, a greater fat infiltrate, and lower metabolic activity at the muscle level, worsening the muscle function. However, more longitudinal studies are needed to analyze changes in muscle quality variables following a physical activity intervention in older people.

Our study has some limitations. The data are limited to community-dwelling older women with sarcopenia. Secondly, there were 13 drop-outs who were excluded from the analysis, with no intention-to-treat analysis to determine the effects. The lower number of participants in the MRI analysis compared to the clinical analysis was due to the restrictive measures imposed by the government during the first lock-down of the COVID-19 pandemic, which also meant that there was no long-term follow-up to analyze the maintenance of the effects obtained after the intervention.

Six months of high-intensity resistance training led to remission of sarcopenia in half of the women who received the intervention. Body composition and muscular function improved, while imaging biomarkers corroborated the clinical outcomes and provided information on muscle quality, showing preserved levels of muscular hydration and a decrease of microscopic fat mass after the intervention.

Contributors

Cristina Flor-Rufino acquired the data, analyzed and interpreted the data and drafted the manuscript.

Joaquin Barrachina-Igual acquired the data, analyzed and interpreted the data and revised the manuscript for key intellectual content.

Pilar Pérez-Ros conceived and designed the study, analyzed and interpreted the data and drafted the manuscript.

Ana Pablos-Monzo conceived and designed the study, analyzed and interpreted the data and drafted the manuscript and revised the manuscript for key intellectual content.

Roberto Sanz-Requena conceived and designed the study, analyzed MRI data and revised the manuscript for key intellectual content.

Francisco M. Martínez-Arnau conceived and designed the study, analyzed and interpreted the data, drafted the manuscript and supervised the study.

Funding

This work was supported by Universitat de València [grant number UV-19-INV_AE19] and *Conselleria de Innovación, Universidades, Ciencia y Sociedad digital*, Valencia, Spain [grant number GV/2020/071]. The sponsor had no role in the design, methods, subject recruitment, data collections, analysis and preparation of paper.

Ethical approval

This study was approved by the Research Ethics Committee of the Universitat de València (H1488746567568), which operates in accordance with the principles of the Declaration of Helsinki. All participants signed the informed consent for participation in the study.

Provenance and peer review

This article was not commissioned and was externally peer reviewed.

Research data (data sharing and collaboration)

There are no linked research data sets for this paper. Data will be made available on request.

Declaration of competing interest

The authors declare that they have no competing interest.

Acknowledgements

The authors thank all participants, Faculty of Physiotherapy of Universitat de València, University of Valencia (Grant UV-19-INV_AE19) and *Conselleria de Innovación, Universidades, Ciencia y Sociedad digital*, Valencia, Spain (Grant GV/2020/071).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.maturitas.2022.09.001.

References

[1] W. World Health Organization, Ageing and health, World Heal. Organ., 2018. https://www.who.int/news-room/fact-sheets/detail/ageing-and-health. (Accessed 18 March 2020).
[2] A.J. Cruz-Jentoft, J.P. Baeyens, J.M. Bauer, Y. Boirie, T. Cederholm, F. Landi, F. C. Martin, J.P. Michel, Y. Rolland, S.M. Schneider, E. Topinková, M. Vandewoude, M. Zamboni, Sarcopenia: European consensus on definition and diagnosis, Age Ageing 39 (2010) 412–423, https://doi.org/10.1093/ageing/afq034.
[3] A.J. Cruz-Jentoft, G. Bahat, J. Bauer, Y. Boirie, O. Bruyère, T. Cederholm, C. Cooper, F. Landi, Y. Rolland, A.A. Sayer, S.M. Schneider, C.C. Sieber, E. Topinkova, M. Vandewoude, M. Visser, M. Zamboni, I. Bautmans, J.P. Baeyens, M. Cesari, A. Cherubini, J. Kanis, M. Maggio, F. Martin, J.P. Michel, K. Pitkala, J. Y. Reginster, R. Rizzoli, D. Sánchez-Rodríguez, J. Schols, Sarcopenia: Revised European consensus on definition and diagnosis, Age Ageing 48 (2019) 16–31, https://doi.org/10.1093/ageing/afy169.
[4] R. Correa-de-Araujo, M.O. Harris-Love, I. Miljkovic, M.S. Fragala, B.W. Anthony, T. M. Manini, The need for standardized assessment of muscle quality in skeletal muscle function deficit and other aging-related muscle dysfunctions: a symposium report, Front. Physiol. 8 (2017) 1–19, https://doi.org/10.3389/fphys.2017.00087.
[5] A. Cruz-Jentoft, Prevalence of and interventions for sarcopenia in ageing adults: a systematic review. Report of the International Sarcopenia Initiative (EWGSOP and IWGS), Age Ageing 43 (2014) 748–759, https://doi.org/10.1093/ageing/afu115.
[6] M.D. Peterson, A. Sen, P.M. Gordon, Influence of resistance exercise on lean body mass in aging adults: a meta-analysis, Med. Sci. Sports Exerc. 43 (2011) 249–258, https://doi.org/10.1249/MSS.0b013e3181eb6265.
[7] M.D. Peterson, M.R. Rhea, A. Sen, P.M. Gordon, Resistance exercise for muscular strength in older adults: a meta-analysis, Ageing Res. Rev. 9 (2010) 226–237, https://doi.org/10.1016/j.arr.2010.03.004.
[8] T.A. Churchward-Venne, M. Tieland, L.B. Verdijk, There are no nonresponders to resistance-type exercise training in older men and women, J. Am. Med. Dir. Assoc. 16 (2015) 400–411.
[9] V.H. Stewart, D.H. Saunders, C.A. Greig, Responsiveness of muscle size and strength to physical training in very elderly people: a systematic review, Scand. J. Med. Sci. Sports 24 (2014) 1–10, https://doi.org/10.1111/sms.12123.
[10] K.M. Lavin, B.M. Roberts, C.S. Fry, T. Moro, B.B. Rasmussen, M.M. Bamman, The importance of resistance exercise training to combat neuromuscular aging, Physiology. 34 (2019) 112–122, https://doi.org/10.1152/physiol.00044.2018.
[11] B.J. Schoenfeld, J. Grgic, D. Ogborn, J.W. Krieger, Strength and hypertrophy adaptations between low- vs. high-load resistance training, J. Strength Cond. Res. 31 (2017) 3508–3523.
[12] J. Steele, J. Fisher, J. Giessing, P. Gentil, Clarity in reporting terminology and definitions of set endpoints in resistance training, Muscle Nerve 56 (2017) 368–374, https://doi.org/10.1002/mus.25557.
[13] R.W. Morton, M.W. Sonne, A. Farias Zuniga, I.Y.Z. Mohammad, A. Jones, C. McGlory, P.J. Keir, J.R. Potvin, S.M. Phillips, Muscle fibre activation is unaffected by load and repetition duration when resistance exercise is performed to task failure, J. Physiol. 597 (2019) 4601–4613, https://doi.org/10.1113/JP278056.
[14] A. Escriche-Escuder, I.J. Fuentes-Abolafio, C. Roldán-Jiménez, A.I. Cuesta-Vargas, Effects of exercise on muscle mass, strength, and physical performance in older adults with sarcopenia: a systematic review and meta-analysis according to the EWGSOP criteria, Exp. Gerontol. 151 (2021), 111420, https://doi.org/10.1016/j.exger.2021.111420.
[15] R. Sanz-Requena, F.M. Martínez-Arnau, A. Pablos-Monzó, C. Flor-Rufino, J. Barrachina-Igual, G. García-Martí, L. Martí-Bonmatí, P. Pérez-Ros, The role of imaging biomarkers in the assessment of sarcopenia, Diagnostics. 10 (2020) 1–14, https://doi.org/10.3390/diagnostics10080534.
[16] N.M. Massy-Westropp, T.K. Gill, A.W. Taylor, R.W. Bohannon, C.L. Hill, Hand grip strength: age and gender stratified normative data in a population-based study, BMC Res. Notes 4 (2011) 127, https://doi.org/10.1186/1756-0500-4-127.
[17] F. Masanés, X. Rojano i Luque, A. Salvà, J.A. Serra-Rexach, I. Artaza, F. Formiga, F. Cuesta, A. López Soto, D. Ruiz, A.J. Cruz-Jentoft, Cut-off points for muscle mass — not grip strength or gait speed — determine variations in sarcopenia prevalence,

J. Nutr. Health Aging 21 (2017) 825–829, https://doi.org/10.1007/s12603-016-0844-5.
[18] H.T. Chen, H.J. Wu, Y.J. Chen, S.Y. Ho, Y.C. Chung, Effects of 8-week kettlebell training on body composition, muscle strength, pulmonary function, and chronic low-grade inflammation in elderly women with sarcopenia, Exp. Gerontol. 112 (2018) 112–118, https://doi.org/10.1016/j.exger.2018.09.015.
[19] M. Cebrià i Iranzo, M. Balasch-Bernat, M. Tortosa-Chuliá, S. Balasch-Parisi, Effects of resistance training of peripheral muscles versus respiratory muscles in older adults with sarcopenia who are institutionalized: a randomized controlled trial, J. Aging Phys. Act. 26 (2018) 637–646, https://doi.org/10.1123/japa.2017-0268.
[20] B.H. Hassan, J. Hewitt, J.W.L. Keogh, S. Bermeo, G. Duque, T.R. Henwood, Impact of resistance training on sarcopenia in nursing care facilities: a pilot study, Geriatr. Nurs. (Minneap.) 37 (2016) 116–121, https://doi.org/10.1016/j.gerinurse.2015.11.001.
[21] M.W. Seo, S.W. Jung, S.W. Kim, J.M. Lee, H.C. Jung, J.K. Song, Effects of 16 weeks of resistance training on muscle quality and muscle growth factors in older adult women with sarcopenia: a randomized controlled trial, Int. J. Environ. Res. Public Health 18 (2021) 1–13, https://doi.org/10.3390/ijerph18136762.
[22] S.B. Cook, D.P. LaRoche, M.R. Villa, H. Barile, T.M. Manini, Blood flow restricted resistance training in older adults at risk of mobility limitations, Exp. Gerontol. 99 (2017) 138–145, https://doi.org/10.1016/j.exger.2017.10.004.
[23] C. De Liao, J.Y. Tsauo, S.W. Huang, J.W. Ku, D.J. Hsiao, T.H. Liou, Effects of elastic band exercise on lean mass and physical capacity in older women with sarcopenic obesity: a randomized controlled trial, Sci. Rep. 8 (2018) 1–13, https://doi.org/10.1038/s41598-018-20677-7.
[24] J.M. del Campo, M.H. Macías, R. Monroy, Effect of a resistance training program on sarcopenia and functionality of the older adults living in a nursing home, J. Nutr. Health Aging 23 (2019) 829–836, https://doi.org/10.1007/s12603-019-1261-3.
[25] C. Beaudart, Y. Rolland, A.J. Cruz-Jentoft, J.M. Bauer, C. Sieber, C. Cooper, N. Al-Daghri, I. Araujo de Carvalho, I. Bautmans, R. Bernabei, O. Bruyère, M. Cesari, A. Cherubini, B. Dawson-Hughes, J.A. Kanis, J.M. Kaufman, F. Landi, S. Maggi, E. McCloskey, J. Petermans, L. Rodriguez Mañas, J.Y. Reginster, R. Roller-Wirnsberger, L.A. Schaap, D. Uebelhart, R. Rizzoli, R.A. Fielding, Assessment of muscle function and physical performance in daily clinical practice: a position paper endorsed by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO), Calcif. Tissue Int. 105 (2019) 1–14, https://doi.org/10.1007/s00223-019-00545-w.
[26] Y. Jeon, M. Shin, C. Kim, B.-J. Lee, S. Kim, D. Chae, J.-H. Park, Y. So, H. Park, C. Lee, B. Kim, J. Chang, Y. Shin, I. Kim, Effect of squat exercises on lung function in elderly women with sarcopenia, J. Clin. Med. 7 (2018) 167, https://doi.org/10.3390/jcm7070167.
[27] A. Grimm, M.D. Nickel, O. Chaudry, M. Uder, F. Jakob, W. Kemmler, H.H. Quick, K. Engelke, Feasibility of Dixon magnetic resonance imaging to quantify effects of physical training on muscle composition—a pilot study in young and healthy men, Eur. J. Radiol. 114 (2019) 160–166, https://doi.org/10.1016/j.ejrad.2019.03.019.
[28] R.L. Marcus, O. Addison, J.P. Kidde, L.E. Dibble, P.C. Lastayo, Skeletal muscle fat infiltration: impact of age, inactivity, and exercise, J. Nutr. Health Aging 14 (2010) 362–366, https://doi.org/10.1007/s12603-009-0230-7.
[29] R. Ramírez-Vélez, Y. Ezzatvar, M. Izquierdo, A. García-Hermoso, Effect of exercise on myosteatosis in adults: a systematic review and meta-analysis, J. Appl. Physiol. 130 (2021) 245–255, https://doi.org/10.1152/JAPPLPHYSIOL.00738.2020.
[30] Y. Yamada, Muscle mass, quality, and composition changes during atrophy and sarcopenia, Adv. Exp. Med. Biol. 1088 (2018) 47–72, https://doi.org/10.1007/978-981-13-1435-3_3.