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ORIGINAL RESEARCH

Muscle Functions in Polymyalgia Rheumatica and Giant-Cell Arteritis

Mikko P. Björkman and Reijo S. Tilvis

Clinics of Internal Medicine and Geriatrics, Helsinki University Central Hospital, POB 340, FI-00290 HUS, Helsinki, Finland. Corresponding author email: mikko.bjorkman@helsinki.fi

Abstract

Objectives: To find out whether and to what extent the muscle functions are impaired in polymyalgia rheumatica (PMR) patients in relation to duration, activity and treatment of the disease as well as any history of giant cell-arteritis (GCA).

Methods: Comprehensive clinical examinations of PMR patients (N = 40) called to participate in a clinical rehabilitation trial included, among others, the polymyalgia rheumatica disease activity score (PMR-AS), cytokine profile, appendicular fat (aFMI) and muscle mass indices (aMMI) by dual X-ray absorbtiometry, mean hand grip strength of both hands (HGS) and force platform countermovement jump height (CJH).

Results: Of the older PMR patients (57.2–80.9 years), five had a history of GCA. Neither aMMI nor aFMI was associated with age in these patients. The HGS correlated moderately with CJH ($r = 0.629$, $P < 0.001$). In multivariate regression analyses, old age ($P = 0.003$), low aMMI ($P = 0.005$), and high aFMI ($P = 0.012$) were independently associated with weak HGS, explaining 62.2% ($R^2 = 0.622$) of its variation. Older age ($P < 0.001$), lower aMMI ($P = 0.001$) and higher aFMI ($P < 0.001$) also independently indicated lower CJH, explaining 75.3% ($R^2 = 0.753$) of its variation. Muscle functions did not associate with disease characteristics of PMR or any history of GCA.

Conclusions: Low muscle mass and adiposity are the most important determinants of impaired muscle function and are a target for prevention in older patients suffering from PMR.

Keywords: polymyalgia rheumatic, giant cell-arteritis, muscle mass, appendicular fat

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Introduction

Polymyalgia rheumatica (PMR) and giant-cell arteritis (GCA) are closely related disorders affecting middle-aged and older people. Both syndromes, which frequently occur together, have unknown causes and have different clinical manifestations.[1,2] Inflammatory processes both in vessels and in connective tissue can cause a wide variation of clinical symptoms in addition to the elevation of acute-phase reactants, including interleukin 6 (IL-6). In GCA, an immune response in the vascular wall initiates a reaction in the artery that leads to structural changes, intimal hyperplasia and luminal occlusion.[3] PMR is characterized by aching and stiffness in the neck, shoulder and pelvic girdles. Distal musculoskeletal manifestations, e.g. symptoms in the knee and wrist, are seen in about half of the patients.[4] Despite the rapid acute response of musculoskeletal aching and stiffness to corticosteroids, residual symptoms may lead to diminished physical activity and impaired muscle function.[5] Long-lasting corticosteroid treatment is often necessary, particularly for GCA, which can further accelerate the loss of bone and muscle tissues.[6] There is some evidence that mitochondrial functions may be deteriorated in muscle cells, leading to diminished production of energy-rich compounds in muscle cells and increased blood lactate,[7] but it has also been shown that skeletal muscle mitochondria remain molecularly and biochemically unaffected, at least in patients recently diagnosed with PMR.[8] However, PMR patients have increased microvascularisation of the deltoid muscle fibers either due to systemic inflammation and the musculoskeletal symptoms or due to the muscle fiber atrophy.[9]

These observations prompted us to hypothesize that both quantitative and qualitative changes occur in the muscle tissues of patients suffering from PMR and GCA, and that the changes are related to the activity, duration and treatment of the disease. In order to test this hypothesis, 40 patients with a diagnosis of PMR were investigated.

Methods

All members of the Helsinki Rheumatoid Association who had a diagnosis of PMR (N = 40) were investigated in a cross-sectional fashion. The study protocol was approved by the local ethics committee and the procedures followed were in accordance with the Helsinki Declaration of 1975, as revised in 1983. All patients provided an informed consent. A postal questionnaire was sent to the patients before the baseline assessment, which included clinical examinations, whole body dual X-ray absorbtiometry (DXA) and blood samples.

Vacuum tubes were used to draw venous blood from patients in a supine position the morning after an overnight fast. In addition to routine analyses, high sensitivity CRP concentration was measured by particle-enhanced immunoturbidimetric assay (Ultrasensitive CRP Kit, Orion Diagnostica, Espoo, Finland) on the Hitachi 917 or Modular (Hitachi Ltd, Tokyo, Japan) automatic analysers (reference range: men: 0.05–2.50 mg/L; women: 0.05–3.00 mg/L). The intra-assay coefficients of variation (CV) were 1.1% at 0.70 mg/L and 0.7% at 5.9 mg/L and the inter-assay coefficients of variation were 6.3% at 0.70 mg/L (N = 22) and 2.2% at 6.6 mg/L (N = 27). The method was accreditated by FINAS Accreditation (SFS-EN ISO/IEC 17025). The plasma concentrations of interleukin 6 (IL-6), interleukin 2 receptor (IL2R) and tumor necrosis factor alpha (TNF-α) were measured using the immunoassay system (Immulite 1000®, Siemens Healthcare Diagnostics, Deerfield, IL, USA) according to the routine instructions of the manufacturer. The levels of detection were 2 ng/L and 4 ng/L for IL-6 and TNF-α, respectively. IL-6 concentrations below the detection limit were considered to be 1.9 ng/L and those of TNF-α to be 3.9 ng/L.

DXA (Prodigy Advance, GE Lunar, Madison, WI) was used to measure whole-body and regional body composition. Whole-body muscle mass (kg) was calculated assuming that all non-fat and non-bone tissue was skeletal muscle. The appendicular muscle mass (kg) was calculated as a sum of muscle in arms and legs. The whole-body fat mass index (FMI) and muscle mass index (MMI), appendicular fat mass index (aFMI) and appendicular muscle mass index (aMMI) were finally determined by dividing the respective mass (kg) with squared height (m^2). All patients were scanned using the standard scan mode. Precisions of the repeated measurements expressed as the percent coefficient of variation were 1.2%, 1.1% and 0.7% for total fat, bone and muscle mass, respectively.

Table 1. Characteristics of polymyalgia rheumatica (PMR) patients by history of giant-cell arteritis (GCA).

Characteristic	No GCA (N = 35)	GCA (N = 5)	*P*-value
Age (years)	72.9 (57.2–80.9)	69.4 (61.8–79.3)	0.800
Men (N (%))	5 (14.3)	0 (0.0)	ND
Charlson comorbidity index >1 (N (%))	12.0 (34.3)	1.0 (20.0)	ND
Number of drugs	5 (1–11)	5 (1–7)	0.588
Continuous five-year corticosteroid therapy (N (%))	18 (51.4)	5 (100.0)	0.061
Time since appearance of PMR symptoms (months)	65 (2–228)	120 (52–168)	0.068
PMR activity score	16.8 (2.0–67.5)	10.7 (4.4–49.5)	0.998
Morning stiffness (minutes)	90 (0–300)	5.0 (0–120)	0.093
Pain (VAS: 0–100)	32 (0–93)	44 (13–83)	0.398
Unusual fatigue (VAS: 0–100)	35 (2–86)	73 (4–96)	0.351
Global health problems (VAS: 0–100)	37 (1–89)	48 (11–68)	0.772
Body mass index (kg/m^2)	26.7 (20.9–34.8)	29.5 (24.8–36.7)	0.261
Fat mass index (kg/m^2)	9.6 (4.5–16.9)	12.2 (10.1–19.0)	0.070
Muscle mass index (kg/m^2)	15.2 (12.5–19.7)	14.2 (13.4–17.3)	0.442
Appendicular fat mass index (kg/m^2)	4.4 (1.8–7.9)	5.5 (4.3–7.3)	0.065
Appendicular muscle mass index (kg/m^2)	6.5 (4.8–8.6)	5.9 (5.7–7.0)	0.520
Mean hand grip strength (kg)	24.5 (13.0–55.5)	16.0 (8.0–39.0)	0.157
Jump height (cm)	10.3 (0.1–26.3)	5.9 (3.3–9.4)	0.069
Relative hand grip strength (kg/kg)	5.7 (3.0–8.3)	4.7 (2.4–8.0)	0.106
Relative jump height (cm/kg)	0.77 (0.01–1.73)	0.56 (0.28–0.67)	0.076
C-reactive protein (mg/L)	3.3 (0.3–65.0)	3.1 (1.6–44.6)	0.721
Erythrocyte sedimentation rate (mm/h)	14.0 (2.0–58)	17.0 (14–53)	0.323
Interleukin 6 (ng/L)	2.8 (1.9–21.8)	4.5 (1.9?6.7)	0.337
Interleukin 2 receptor (kU/L)	480 (204–907)	429 (372–638)	0.879
Tumor necrosis factor α (ng/L)	5.9 (3.9–13.5)	5.2 (4.5–7.0)	0.397

Values are the median (minimum—maximum) unless otherwise indicated.
Abbreviations: ND, not determined due to low numbers; VAS, visual analog scale.

Muscle functions were measured by hand grip strength and countermovement jump height (CJH). Hand grip strength (kg) of both hands was measured twice in a sitting position with a 30-second rest after each attempt using a JAMAR hydraulic hand dynamometer (Saehan Corp., Masan, Korea).[10] The results were rounded to the nearest kg and the best result was selected to calculate the mean hand grip strength (HGS) of both hands. The validity of HGS using the best of three approach has been extensively studied in representative elderly populations.[11–13] The measurement of jump height was based on jump time during a countermovement jump, recorded by a force platform (HurLabs, Tampere, Finland). Patients were instructed to keep their hands on their waist during each jump. The highest jump (cm) of the three attempts with a 30-second interval was selected. Finally, relative HGS (kg) and CJH (cm) were calculated by dividing them with muscle mass (kg) of the upper and lower limbs, respectively. One patient declined to perform the jump test because of an unspecified lower back problem that caused pain during and after jumps.

The PMR disease activity score (PMR-AS) was calculated as the sum of pain intensity measured by a 100 mm visual analog scale (VAS), C-reactive protein concentration (mg/L), duration of morning stiffness (minutes) and ability to elevate the upper limbs (0–3).[10] The values for pain intensity VAS and duration of morning stiffness were divided by ten before the calculation of PMR-AS. The level (0–3) of the semiquantitative 'elevation of upper limbs' scale was determined as: 3 = no upper limb elevation, 2 = elevation below the shoulder girdle, 1 = elevation up to the shoulder girdle and 0 = elevation above the shoulder girdle. PMR-AS scores above 17 was considered high, scores above 7 were moderate and scores below 7 suggested low

disease activity.[14] The physician's global assessment was not included in the PMR-AS in the present study.

Comorbidity of patients was evaluated by the Charlson comorbidity index score.[15] A multidimensional health assessment questionnaire (MDHAQ) was also used.[16,17] The MDHAQ included among others visual analog scale for unusual fatigue during the preceding week and for global health problems.

The data were analyzed using Windows SPSS (SPSS for Windows 16.0, Chicago: SPSS Inc.). Bivariate correlation was used to compute the Pearson's correlation coefficients and their level of significance. Chi-square tests were used for dichotomous and independent samples, and the t-test for continuous variables in the univariate analyses. The Mann—Whitney u-test was used instead of the t-test if the continuous variables had a skewed distribution according to the one-sample Kolmogorov—Smirnov test. HGS and CJH were selected as dependent variables for multivariate analysis. Thus, the patients were stratified by median HGS and CJH (crude and relative), and variables with *P*-values below 0.100 were entered as independent values into the multivariate linear regression models in order to determine β-values and their level of significance for each independent variable. Natural logarithmic or square root transformations of variables with skewed distribution were used in multivariate models to ensure normal distribution of variables. P-values below 0.050 were considered significant.

Results

Characteristics of patients

Of the older PMR patients (N = 40, age 57.2–80.9 years), five had a history of GCA (Table 1). All of them were women and had received continuous corticosteroid therapy during the previous five years. The patients with a history of GCA also tended to have a shorter duration of morning stiffness, a longer PMR history, poorer muscle functions and greater fat mass. However, the muscle masses and cytokine profiles were very similar in both groups. No significant correlation of MMI, aMMI, FMI or aFMI in relation to age was found.

Upper limb muscle functions

HGS correlated quite closely with MMI (r = 0.552, $P < 0.001$) and aMMI (r = 0.602, $P < 0.001$). The respective correlations with FMI (r = –0.326, $P = 0.040$) and aFMI (r = –0.464, $P = 0.003$) were inverse. HGS was almost twice as high in men as in women (mean 39.9 vs. 22.6 kg; $P < 0.001$). The gender differences in the relative HGS scores were insignificant (mean 6.6 vs. 5.6 kg/kg; $P = 0.125$), but these values decreased with advancing age (r = –0.337, $P = 0.033$) (Fig. 1 Panel A). Relative HGS was inversely associated with FMI (r = –365, $P = 0.021$) and also with aFMI (r = –0.455, $P = 0.003$) (Fig. 2 Panel A).

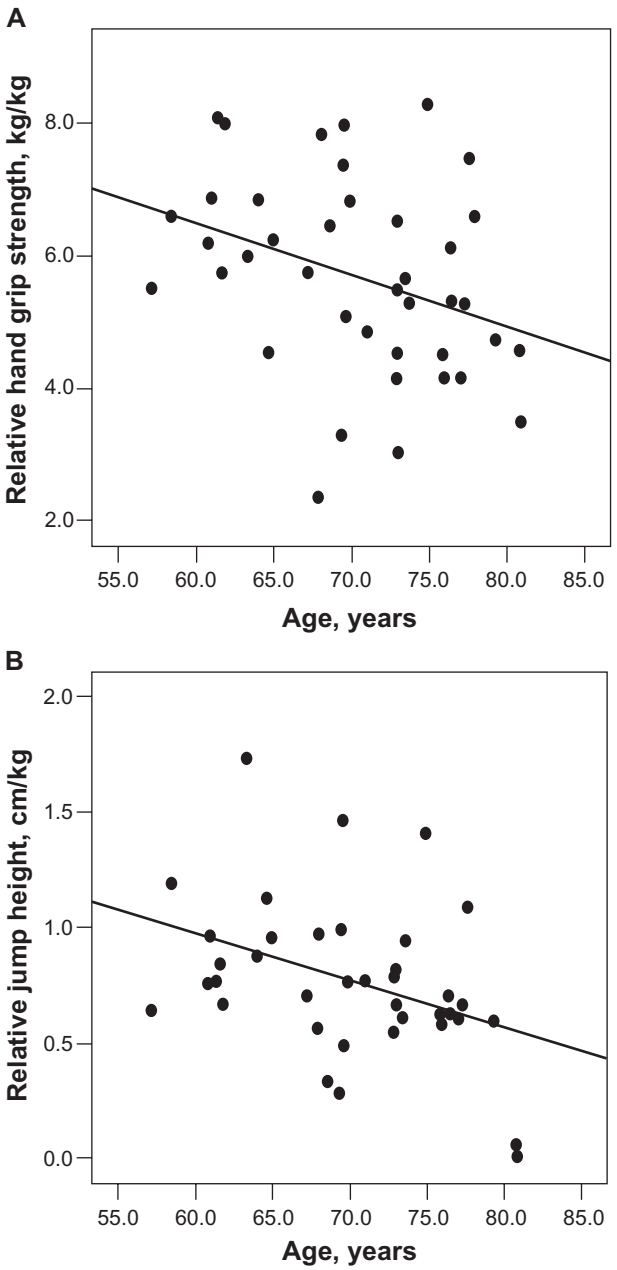

Figure 1. Association of age with mean HGS of both hands related to muscle mass of upper limbs (**A**: r = –0.337, $P = 0.033$) and CJH related to muscle mass of lower limbs (**B**: r = –0.385, $P = 0.015$).

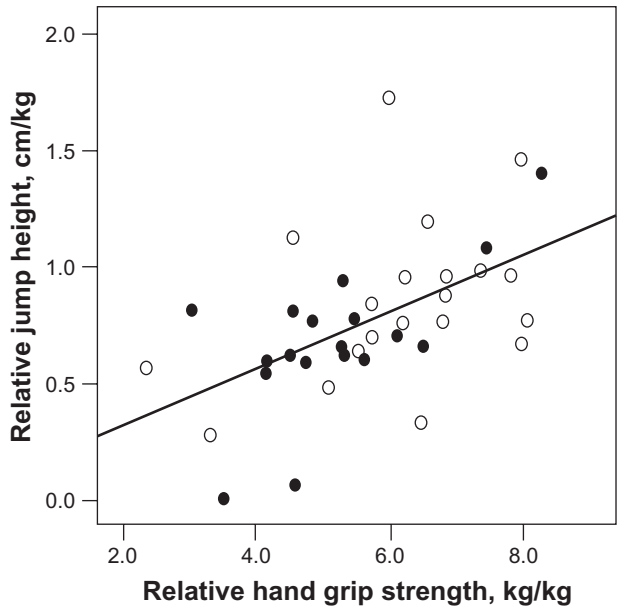

Figure 2. Association between mean HGS of both hands related to muscle mass of upper limbs and CJH related to muscle mass of lower limbs (r = 0.534, $P = 0.001$). Markers set by median age (open circles <70.4 years; solid circles ≥70.4 years).

However, HGS did not associate significantly with the length of PMR history, corticosteroid therapy, pain, duration of morning stiffness, disease activity score or actual cytokine profile (Table 2). This was also true for relative HGS (data not shown). In the multivariate regression analyses, old age (standardized $\beta = -0.277$, $P = 0.012$), low aMMI (standardized $\beta = 0.542$, $P < 0.001$), and high aFMI (standardized $\beta = -0.471$, $P < 0.001$) associated independently with weak HGS, explaining 62.2% ($R^2 = 0.622$) of its variation.

Lower limb muscle functions

HGS and CJH (r = 0.656, $P < 0.001$) as well as their relative values (r = 0.534, $P < 0.001$) correlated moderately (Fig. 2). Men tended to have better relative CJH than women (mean 0.97 vs. 0.74 cm/kg; $P = 0.158$). Relative CJH also decreased significantly with age (r = –0.385, $P = 0.015$) (Fig. 3 Panel A) and was associated inversely with FMI (r = –0.461, $P = 0.003$) as well as aFMI (r = –0.550, $P < 0.001$) (Fig. 3 Panel B). Again, no statistically significant associations were found with the disease characteristics of PMR (Table 2). Again, older age (standardized $\beta = -0.363$, $P < 0.001$), lower aMMI (standardized $\beta = 0.502$, $P = 0.001$) and higher aFMI (standardized $\beta = -0.597$, $P < 0.001$) also

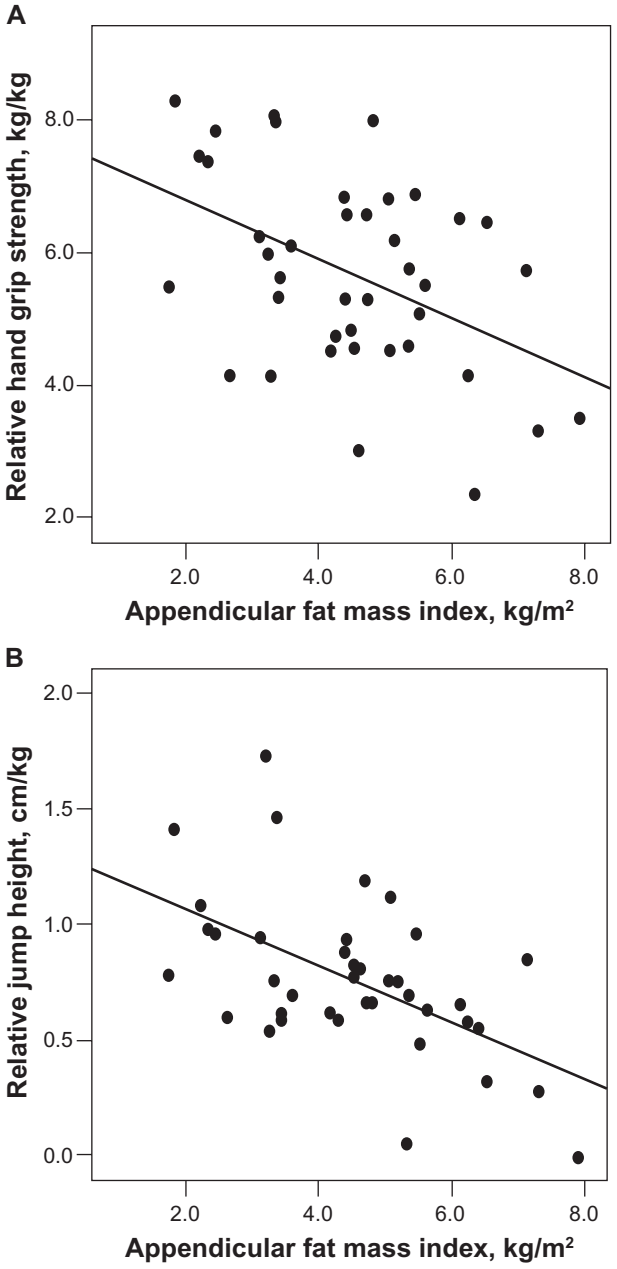

Figure 3. Association of appendicular fat mass index with mean HGS of both hands related to muscle mass of upper limbs (**A**: r = –0.455, $P = 0.003$) and CJH related to muscle mass of lower limbs (**B**: r = –0.550, $P < 0.001$).

independently indicated lower CJH, explaining 75.3% ($R^2 = 0.753$) of its variation.

Discussion

Our data show that in addition to muscularity, age-associated decreases in the muscle function of both upper and lower extremities are consistently related to body fat, particularly adiposity of the arms and legs, and that these phenomena surpass more

Table 2. Disease characteristics of polymyalgia rheumatica (PMR) and body composition by median values of hand grip strength (HGS) (23.75 kg) and countermovement jump height (CJH) (9.44 cm).

Variable	HGS			CJH		
	Low (N = 20)	High (N = 20)	*P*-value	Low (N = 19)	High (N = 20)	*P*-value
Age (years)	73.0 (58.4–80.9)	67.6 (57.2–77.6)	0.015	73.0 (61.3–80.9)	66.5 (57.2–77.6)	0.002
Men (N (%))	0 (0.0)	5 (25.0)	0.047	0 (0.0)	5 (25.0)	0.047
Charlson comorbidity index >1 (N(%))	5 (25.0)	8 (40.0)	0.501	7 (36.8)	6 (30.0)	0.651
Number of drugs	5.0 (1–9)	5.5 (1–11)	0.402	6.0 (2–11)	5.0 (1–9)	0.139
Current corticosteroid medication (N(%))	18 (90.0)	17 (85.0)	ND	17 (89.5)	17 (85.0)	ND
Weekly corticosteroid dose (mg)	32.5 (0–105)	27.5 (0–175)	0.512	35.0 (0–70)	27.5 (0–175)	0.513
Continuous 5-year corticosteroid therapy (N (%))	9 (45.0)	14 (70.0)	0.110	12 (63.2)	11 (55.0)	0.605
History of giant cell arteritis (N (%))	4 (20.0)	1 (5.0)	0.342	4 (21.1)	1 (5.0)	0.182
Time since appearance of PMR symptoms (months)	62.5 (2.0–168)	78 (30–228)	0.239	72 (26–192)	63 (2.0–228)	0.586
PMR activity score	16.5 (2.2–49.5)	16.5 (2.0–67.5)	0.581	16.8 (2.2–49.5)	16.7 (2.0–67.5)	0.646
Morning stiffness (minutes)	75 (0–180)	75 (0–300)	0.604	90 (0–300)	60 (0–300)	0.279
Pain (VAS: 0–100)	31 (0–61)	33 (3–93)	0.268	32 (0–93)	34 (3–83)	0.981
Unusual fatigue (VAS: 0–100)	32.5 (4–86)	43 (2–96)	0.884	43 (4–85)	38 (2–96)	0.812
Global health problems (VAS: 0–100)	42.5 (1–89)	35 (3–82)	0.853	40 (1–89)	33 (3–82)	0.415
C-reactive protein (mg/L)	3.2 (0.3–44.6)	3.3 (0.7–65.0)	0.862	2.8 (0.3–44.6)	3.3 (1.2–65.0)	0.107
Erythrocyte sedimentation rate (mm/h)	17.0 (4.0–53)	12.5 (2.0–58)	0.227	17.0 (4.0–53)	13.5 (2.0–58)	0.645
Interleukin 6 (ng/L)	2.8 (1.9–21.8)	3.0 (1.9–18.1)	0.414	2.8 (1.9–21.8)	3.3 (1.9–18.1)	0.687
Interleukin 2 receptor (kU/L)	466 (333–736)	498 (204–907)	0.750	486 (204–907)	442 (219–772)	0.352
Tumor necrosis factor α (ng/L)	5.9 (3.9–13.5)	5.7 (3.9–11.9)	0.889	6.1 (3.9–11.9)	5.5 (3.9–13.5)	0.916
Body mass index (kg/m^2)	27.3 (20.9–36.7)	26.2 (20.9–34.8)	0.788	26.4 (20.9–36.7)	27.9 (20.9–34.8)	0.948
Fat mass index (kg/m^2)	11.3 (5.9–19.0)	8.3 (4.5–16.9)	0.095	11.3 (6.4–19.0)	9.9 (4.5–14.5)	0.128
Muscle mass index (kg/m^2)	14.6 (12.5–18.0)	15.9 (13.0–19.7)	0.006	14.7 (12.5–18.0)	15.9 (13.7–19.7)	0.005
Appendicular fat mass index (kg/m^2)	4.7 (2.4–7.9)	3.5 (1.8–6.5)	0.014	4.7 (3.3–7.9)	4.4 (1.8–7.1)	0.025
Appendicular muscle mass index (kg/m^2)	5.9 (4.8–7.6)	6.8 (5.2–8.6)	0.002	6.0 (4.8–7.6)	6.9 (5.3–8.6)	0.002

Values are the median (minimum—maximum) unless otherwise indicated.
Abbreviations: VAS, visual analog scale. ND, not determined due to low numbers.

significant than the possible deleterious effects of the disease in PMR patients at a stable stage. Contrary to our hypothesis, the muscle performance and functioning of PMR patients was not related to the duration and severity of the disease. This observation suggests that the long-term harmful effects of PMR are relatively small compared with age-related anthropometric changes. Although the negative results from our relatively small sample should be interpreted with caution, the consistency of the results supports credibility. Furthermore, the proportion of GCA cases among these PMR patients corresponds well to that observed in larger population studies.[1] However, it is quite possible that muscle strength is affected during acute flares of PMR, but our series did not include acute patients seeking advice. In fact, in view of the low levels of inflammatory markers, e.g. the cytokine profile, the activity of PMR was low.

The age-associated decline in muscle function in PMR patients aged 57–81 years is in good accordance with earlier studies on different population.[18,19] However, neither the amount of muscle nor fat tissue was associated with age in this series of patients, but both age and fat mass turned to be strong, independent indicators of impaired lower limb muscle performance. This mismatch between age-associated decline in muscle mass and function fits well with the results from previous studies[20,21] and is based on multifaceted progressive deterioration of muscle quality.[22]

Our results emphasize the role of fat in impaired muscle performance and support the view that fat infiltration into muscles is an important factor impairing muscle quality,[22,23] especially because of close inverse relationships between muscle function and the amount of fat in the extremities. The inverse association between fat mass and muscle strength has been earlier found in both in the general population[24–28] and in patients with rheumatic diseases.[29,30] Apart from the substitution of muscle fibers by fat cells, low muscle strength and adiposity share common etiopathogenesis, including low physical activity, hormonal changes and features of chronic inflammation.[22,23]

This study used CJH as an indicator of lower limb muscle performance. It can be argued that the patients who were not able to jump as high were simply heavier. This would also explain the correlation between CJH and adiposity in the present study. However, the BMI was very similar among both the higher and lower jumpers and a statistically significant difference in BMI was not found. This observation further underlines the relevance of our results.

From the practical point of view, our results indicate that adiposity is an important determinant of impaired muscle function and is a target for prevention in older patients suffering from PMR.

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Disclosures

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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