

INTERSTITIAL LUNG DISEASE

Skeletal muscle weakness in patients with sarcoidosis and its relationship with exercise intolerance and reduced health status

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Thorax 2005;60:32–38. doi: 10.1136/thx.2004.022244

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Received 26 January 2004
Accepted 28 May 2004

Background: Skeletal muscle weakness is assumed to be present in patients with sarcoidosis but has never been reported in a consecutive group of patients. Moreover, its relationship with previously observed exercise intolerance and reduced health status has never been studied in these patients.

Methods: Pulmonary function, skeletal and respiratory muscle forces, peak and functional exercise capacity, health status, and the circulating levels of inflammatory and anabolic markers were determined in 25 patients with sarcoidosis who complained of fatigue (15 men) and in 21 healthy subjects (13 men).

Results: Patients with sarcoidosis had lower respiratory and skeletal muscle forces, reduced exercise capacity and health status, higher anxiety and depression scores, and higher circulating levels of tumour necrosis factor- α than healthy subjects (all $p \leq 0.01$). Its soluble receptor p75 tended to be higher ($p = 0.04$). Circulating levels of interleukin (IL)-6, IL-8, insulin-like growth factor I and its binding protein 3 were not significantly different between the two groups. Skeletal muscle weakness was related to exercise intolerance, depression, and reduced health status in patients with sarcoidosis, irrespective of age, sex, body weight and height ($p \leq 0.05$). Quadriceps peak torque was inversely related to fatigue but not to the circulating levels of inflammatory or anabolic markers. The mean daily dose of corticosteroids received in the 6 month period before testing was related to quadriceps peak torque only in patients who received oral corticosteroids.

Conclusion: Skeletal muscle weakness occurs in patients with sarcoidosis who complain of fatigue and is associated with reduced health status and exercise intolerance.

Sarcoidosis is a heterogeneous multisystem disorder of unknown aetiology which often presents with bilateral hilar lymphadenopathy, pulmonary infiltration, and ocular and skin lesions.¹ In addition to possible changes in forced vital capacity (FVC) and carbon monoxide transfer factor (Tlco), a higher prevalence of clinical depression,^{2,3} reduced health status^{3–5} and exercise intolerance^{6–10} have been observed in patients with sarcoidosis.

Reduced health status has been related to decreased pulmonary function,⁴ depressive symptoms,³ and to respiratory muscle weakness.⁵ Exercise capacity is believed to be limited by dyspnoea, an insufficient heart rate response, decreased arterial oxygen tension during exercise, excessive and inefficient ventilation, and by respiratory muscle weakness.^{5,7,8,10} In the past exercise capacity was shown to be limited by skeletal muscle weakness in patients with chronic pulmonary or cardiac disease.^{11,12} The possible contribution of skeletal muscle weakness to exercise intolerance has never been studied in patients with sarcoidosis. Although Wirmsberger *et al*⁵ found that quadriceps muscle force and handgrip force of patients with sarcoidosis were not significantly different from healthy subjects, 67% of the sarcoidosis patients studied by Miller *et al* terminated their peak exercise test due to "leg complaints".⁹ Skeletal muscle weakness is therefore still assumed to be present in patients with sarcoidosis.¹ Treatment with oral corticosteroids,¹³ clinical symptoms of depression,^{2,3} myositis,¹⁴ self-reported complaints of fatigue,¹⁵ and high circulating levels of tumour necrosis factor- α (TNF- α)¹⁶ are all present in patients with sarcoidosis and can all affect skeletal muscle force and exercise capacity.^{17–22} Additionally, low levels of circulating

insulin-like growth factor I (IGF-I), which can be induced by high levels of TNF- α ,²³ and high circulating levels of interleukin (IL)-6 and IL-8 (CXCL8) have been associated with skeletal muscle weakness.^{24,25} These interleukins are part of the current concept of the immunopathogenesis of sarcoidosis¹⁶ and may be raised in patients with stable sarcoidosis.²⁶

Based on these findings, we reasoned that skeletal muscle weakness may be present in patients with sarcoidosis who complain of fatigue and may be related to exercise capacity, symptoms, and to health status. A cross sectional comparative study was therefore undertaken to investigate three questions:

- Is skeletal muscle weakness present in sarcoidosis patients with fatigue compared with healthy control subjects?
- What is the relationship between skeletal muscle force and exercise capacity and health status?
- What is the relationship between skeletal muscle force and circulating levels of inflammatory and anabolic markers and the use of oral corticosteroids?

METHODS

Participants

Twenty nine consecutive patients with sarcoidosis who spontaneously complained of fatigue at the outpatient interstitial lung disease clinic in a tertiary care setting (without being asked by the pulmonary physicians) received information about the survey and were invited to participate. Sarcoidosis had been previously diagnosed according to the

latest ATS/ERS/WASOG statement on sarcoidosis.¹ Twenty five patients agreed to participate, of which 22 were eligible for statistical analyses. One patient with clinical symptoms of severe cox arthrosis and two patients with electrocardiographic evidence of cardiac dysfunction during peak exercise were excluded. Sarcoidosis had been diagnosed a median of 4 years previously (IQR 2–7). Based on their chest radiographs, seven patients had stage I disease, six had stage II, and nine had stage III.²⁷ None of the patients had any significant medical history or co-morbidity except for one man who was known to have diabetes mellitus type 2. Fifty percent of the patients received oral corticosteroids in the 6 month period before testing at a mean dose of 1–32 mg oral methylprednisolone equivalents per day.

Twenty one age and sex matched healthy subjects were recruited from relatives and friends by two students of the Faculty of Physical Education and Physiotherapy (table 1).

The ethics committee of the University Hospitals Leuven granted approval for the study. All participants were of white ethnic origin and gave oral and written informed consent.

Blood analyses

Venous blood was drawn from supine subjects between 08.30 and 09.00 hours before functional testing. IL-6 and CXCL8 were determined using cytometric bead array, TNF- α and its soluble receptors (sTNF-R55 and sTNF-R75) were measured using enzyme linked immunoassays, IGF-I was determined using a radioimmunoassay as described previously,²⁸ and IGF binding protein-3 (IGFBP-3) was assessed using an immunoradiometric assay.

Functional tests

Pulmonary function, respiratory muscle forces, handgrip force, quadriceps peak torque, and 6 minute walking distance were measured as described previously.^{12, 29} Peak exercise capacity was assessed by a maximal incremental cycle exercise test. After a 2 minute resting period and 3 minutes of unloaded cycling, participants started at 20 watts and cycled until symptom limitation at an incremental workload (+30 watt/2 minutes). At the end of the test Borg symptom scores for dyspnoea and fatigue were obtained from all participants. Peak external work rate and peak oxygen uptake were normalised for height, age, and sex.³⁰

Questionnaires

Health status was measured using the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36)³¹ and the EQ-5D (formerly the EuroQoL).³² The Hospital Anxiety and

Depression Scale (HADS)³³ and the domain fatigue of the Chronic Respiratory Disease Questionnaire (CRDQ)³⁴ were used to assess the presence of clinical symptoms of anxiety, depression and fatigue, respectively.

Statistical analyses

The results are presented as mean (SD) or median (interquartile range, IQR). A two tailed unpaired *t* test (continuous), a Mann-Whitney U test, or a χ^2 test (binomial) was used to determine differences between sarcoidosis patients and healthy subjects. Differences between means and their 95% confidence intervals (95% CI) are reported. Moreover, differences between medians and their 95% CI were calculated based on the resampling technique known as bootstrap. The number of replicates was set equal to 5000.³⁵ A priori, a two sided level of significance was set at $p \leq 0.01$.³⁶ Pearson product moment correlation (continuous, *r*) or Spearman rank correlation (*r_s*) were used to determine relationships in patients with sarcoidosis. A priori, a two sided level of significance was set at $p \leq 0.05$.³⁶

RESULTS

Cross sectional comparisons

Characteristics and functional tests

Patients with sarcoidosis generally had normal body mass index (BMI) and spirometric test results, mildly reduced TLCO (difference between means 15% predicted (95% CI 7 to 23), $p = 0.02$), normal PaO₂ and PaCO₂ (table 1), and lower respiratory and skeletal muscle force (table 2).

Functional and peak exercise capacity were lower in patients with sarcoidosis than in healthy subjects (table 2). On average, patients reached the limits of their cardiocirculatory system (defined as: 220 – age (expressed in years) \pm 15 beats per minute), accompanied by high Borg symptom scores for dyspnoea and fatigue (table 2). Patients and healthy subjects had comparable linear relationships between mean oxygen uptake and mean external work rate (oxygen consumption = 0.3985 + 0.0090 \times external work rate versus 0.3505 + 0.0095 \times external work rate, respectively). In contrast, the slope of the linear relationship between mean heart rate and mean oxygen consumption tended to be significantly steeper in patients with sarcoidosis ($p = 0.09$, see fig S1 online).

Circulating levels of inflammatory and anabolic markers

Only the median circulating level of TNF- α was significantly higher in patients with sarcoidosis (24.1 pg/ml (IQR 20.2–30.5)) than in healthy subjects (15.3 pg/ml (IQR 12.9–22.5)). Moreover, there was a tendency for sTNF-R75 to be higher in patients with sarcoidosis (median 4.35 ng/ml (IQR 3.83–4.95)) than in healthy subjects (median 3.54 ng/ml (IQR 2.72–4.42), $p = 0.04$). Complete results are shown in table S1 in the online Appendix.

Questionnaires

Patients scored significantly worse on the CRDQ domain fatigue (median 15 points (IQR 11–17)) than healthy subjects (median 24 (IQR 23–26), $p = 0.0001$; difference between medians 9 points (95% CI 7 to 13)). Compared with healthy subjects, the health status of patients with sarcoidosis was significantly lower (table 3). Patients reported some or severe problems with performing usual activities and more pain and discomfort on the EQ-5D than healthy subjects (table 3). Patients had significantly higher median scores for anxiety and depression on the HADS (table 3); 24% of the patients scored above the cut off score of 10 points for clinical anxiety and 38% for depression. No healthy subject scored ≥ 10 points.

Table 1 Characteristics of study subjects

	Sarcoidosis	Healthy subjects
Sex (M:F)	14:8	13:8
Age (years)	42 (9)	42 (10)
Smoking (never/ex/current)	12/9/1	11/7/3
Height (cm)	172 (9)	172 (9)
BMI (kg/m ²)	27 (5)	25 (4)
FVC (l)	4.30 (1.37)	4.81 (1.39)
FVC (% predicted)	101 (19)	114 (16)
FEV ₁ /FVC (%)	77 (8)	79 (7)
TLCO (mmol/min/kPa)*	7.92 (2.19)	9.35 (2.05)
TLCO (% predicted)**	77 (15)	93 (12)
PaO ₂ (kPa)	12.3 (1.2)	12.9 (0.9)
PaCO ₂ (kPa)**	5.2 (0.5)	5.6 (0.5)

Values are expressed as mean (SD) except for sex and smoking history (absolute numbers).

BMI, body mass index; FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 second; TLCO, carbon monoxide transfer factor;

PaO₂, arterial oxygen tension; PaCO₂, arterial carbon dioxide tension.

* $p = 0.03$; ** $p < 0.01$.

Table 2 Muscle force and exercise capacity in patients with sarcoidosis and healthy subjects

	Sarcoidosis	Healthy subjects	Differences between means (95% CI)	p value
Muscle force				
P _{imax} (cm H ₂ O)	-89 (31)	-115 (33)	-26 (-45 to -5)	0.01
P _{imax} (% predicted)	79 (21)	104 (28)	25 (10 to 40)	0.002
P _{emax} (cm H ₂ O)	157 (53)	205 (53)	49 (16 to 81)	0.004
P _{emax} (% predicted)	84 (20)	112 (19)	28 (16 to 40)	0.0001
HGF (kgF)	38 (13)	45 (13)	7 (-1 to 16)	0.07
HGF (% predicted)	87 (22)	104 (16)	17 (5 to 28)	0.007
QPT (Nm)	142 (62)	187 (56)	45 (9 to 81)	0.02
QPT (% predicted)	67 (22)	95 (16)	29 (17 to 41)	0.0001
Functional exercise test				
ΔMWD (m)	605 (131)	788 (106)	183 (109 to 256)	0.0001
ΔMWD (% predicted)	79 (13)	102 (11)	23 (16 to 31)	0.0001
Dyspnoea ΔMWD (points)	3.7 (1.8)	1.9 (1.2)	-1.8 (-2.7 to -0.8)	0.0006
Fatigue ΔMWD (points)	4.6 (2.5)	3.6 (1.7)	-0.9 (-2.2 to 0.4)	0.18
Peak exercise test				
Peak load (watt)	165 (54)	230 (72)	65 (26 to 104)	0.002
Peak load (% predicted)	84 (17)	123 (22)	40 (28 to 52)	0.0001
Peak V _{O₂} (ml/kg/min)	25 (9)	36 (10)	11 (5 to 17)	0.001
Peak V _{O₂} (% predicted)	85 (24)	109 (15)	24 (12 to 37)	0.0003
Peak HR (% HR _{max} pred)	95 (9)	101 (6)	6 (1 to 11)	0.02
Peak V _E (% MVV)	74 (17)	71 (12)	-3 (-12 to 6)	0.53
Lactate (mmol/l)	9.8 (2.9)	11.7 (3.1)	1.9 (-0.2 to 4.0)	0.08
Dyspnoea cycle (points)	5.9 (1.9)	4.9 (2.0)	-1.0 (-2.2 to 0.3)	0.14
Fatigue cycle (points)	7.4 (1.9)	6.3 (1.6)	-1.1 (-2.2 to 0.0)	0.05

Values are expressed as mean (SD) and as the differences between means (with 95% CI). P_{imax}, maximal inspiratory pressure; P_{emax}, maximal expiratory pressure; HGF, handgrip force; kgF, kilogram force; QPT, quadriceps peak torque; Nm, Newton-meter; ΔMWD, distance walked in 6 minutes; V_{O₂}, oxygen uptake; HR, heart rate; % HR_{max} pred, percentage of maximal heart rate predicted; V_E, ventilation; MVV, maximum voluntary ventilation.

Steroids v non-steroids in sarcoidosis

Patients with sarcoidosis who were treated with corticosteroids in the 6 month period before testing ($n = 11$, median 5 mg/day (IQR 2–18)) and those who were not ($n = 11$) had comparable characteristics, muscle force (fig 3), and exercise capacity except for FVC (table 4) and IL-6 (table S2 in the online Appendix). Moreover, TNF- α and the SF-36 scale physical functioning tended to be different (table S3 in the online Appendix). When only the 11 patients with sarcoidosis who had not received oral corticosteroids in the 6 month period before testing were considered, there was still a reduction in quadriceps peak torque compared with healthy subjects ($p < 0.01$).

Correlations

Correlations between functional tests in sarcoidosis
To reduce the impact of confounding variables on the correlations, the values of the functional tests were normalised

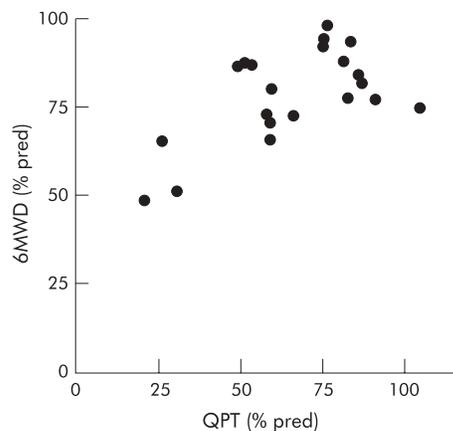


Figure 1 Correlation between muscle force and functional exercise capacity in patients with sarcoidosis. There was a positive correlation between quadriceps peak torque (QPT) and the distance walked in 6 minutes (ΔMWD) in patients with sarcoidosis. Both variables are expressed as a percentage of the predicted values (% pred).

for age, sex, height, and/or body weight by expressing them as a percent of the predicted values. Quadriceps peak torque was significantly associated with peak external work rate ($r = 0.47$, $p = 0.03$), the timed walking distance ($r = 0.61$, $p = 0.003$, fig 1), and with the Borg symptom scores for fatigue after the peak exercise test ($r_s = -0.43$, $p = 0.05$) and functional exercise test ($r_s = -0.75$, $p = 0.0001$). Neither FVC nor T_{lco} were correlated with peak external work rate ($r = 0.38$, $p = 0.08$ and $r = 0.37$, $p = 0.09$, respectively) or with the timed walking distance ($r = -0.01$, $p = 0.97$; and $r = 0.18$, $p = 0.42$, respectively).

Correlations between functional tests, depression, and health status in sarcoidosis

Quadriceps peak torque was inversely correlated with depression ($r_s = -0.50$, $p = 0.02$). In addition, positive correlations were found with SF-36 scales physical functioning ($r_s = 0.70$, $p = 0.0004$, fig 2), physical role ($r_s = 0.59$, $p = 0.006$), pain ($r_s = 0.62$, $p = 0.003$), vitality ($r_s = 0.44$, $p = 0.04$), social functioning ($r_s = 0.50$, $p = 0.02$), and mental health ($r_s = 0.56$, $p = 0.01$), and with the CRDQ domain fatigue ($r_s = 0.48$, $p = 0.03$).

Neither FVC nor T_{lco} was correlated with depression ($r_s = -0.07$, $p = 0.77$; and $r_s = -0.25$, $p = 0.27$, respectively) or with the CRDQ domain fatigue ($r_s = 0.18$, $p = 0.45$; and $r_s = 0.26$, $p = 0.27$, respectively), and they were only positively related to one SF-36 multiple item scale: physical functioning ($r_s = 0.46$, $p = 0.04$, and $r_s = 0.42$, $p = 0.056$, respectively).

Depression and fatigue correlated strongly with most of the SF-36 scales, especially with those that indicate the extent to which physical health or emotional problems interfere with normal social activities (tables 4 in the online Appendix).

Correlations with circulating anabolic and inflammatory markers in sarcoidosis

Only IGF-I was positively related to maximal inspiratory pressure (expressed as % predicted, $r_s = 0.45$, $p = 0.04$). Neither respiratory muscle forces nor skeletal muscle forces

Table 3 Scores on questionnaires in patients with sarcoidosis and healthy subjects

	Sarcoidosis	Healthy subjects	Differences between medians (95% CI)	p value
SF-36 (0–100)				
Physical functioning	45 (35–70)	95 (90–100)	50 (25 to 65)	0.0001
Role functioning physical	0 (0–50)	100 (100–100)	100 (50 to 100)	0.0001
Bodily pain	50 (40–60)	80 (70–100)	30 (20 to 60)	0.0009
General health	30 (20–60)	80 (65–85)	50 (15 to 60)	0.0001
Vitality	45 (30–60)	80 (65–85)	35 (15 to 50)	0.0001
Social functioning	62.5 (50–88)	100 (88–100)	37.5 (12.5 to 50)	0.0002
Role functioning emotional	100 (33–100)	100 (100–100)	0 (0 to 33.3)	0.02
Mental health	64 (44–80)	88 (80–92)	24 (4 to 44)	0.0001
EQ-5D (none/some or severe)				
Mobility	14/8	19/1	–	0.02
Self-care	19/3	20/0	–	0.095
Usual activities	7/15	19/1	–	0.001
Pain/discomfort	4/18	16/4	–	0.001
Anxiety/depression	15/7	18/2	–	0.101
Visual analogue scale	65 (40–85)	83 (66–97)	18 (7 to 30)	0.0001
HADS (0–21)				
Anxiety	7 (5–10)	3 (1–5)	–4 (–8 to –2)	0.0002
Depression	7 (3–11)	0 (0–1)	–7 (–11 to –3)	0.0001

Values are expressed as median (interquartile range) and as differences between medians (95% CI). Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) included eight multiple item scales. Scores can range from 0 (worst) to 100 (optimal). The Hospital Anxiety and Depression Scale (HADS) included seven questions related to anxiety and seven related to depression. Each item is rated on 4-point scale (0–3) giving maximum scores of 21 for anxiety and depression, respectively. A score of >10 points is suggestive for the clinical presence of anxiety or depression. EQ-5D is expressed as a number of patients or healthy subjects who have none or some or severe problems on the five domains. n=20 healthy subjects for all questionnaires.

were significantly related to IGFBP-3, IL-6, CXCL8, TNF- α , or to its receptors.

Correlations with mean daily dose of corticosteroids in sarcoidosis

Only in the patients who received oral corticosteroid treatment was quadriceps peak torque inversely related to the mean daily dose of corticosteroids received in the 6 months before testing (n = 11, $r_s = -0.62$, p = 0.04, fig 3). Maximal inspiratory pressure ($r_s = 0.33$), expiratory pressure ($r_s = -0.24$), and handgrip force ($r_s = -0.46$) were not related to the mean daily dose of corticosteroids in these patients (p>0.15).

DISCUSSION

This study is the first to show significant reductions in skeletal muscle force in patients of white ethnic origin with sarcoidosis who complain of fatigue accompanied by exercise intolerance, depression, and reduced health status. In fact,

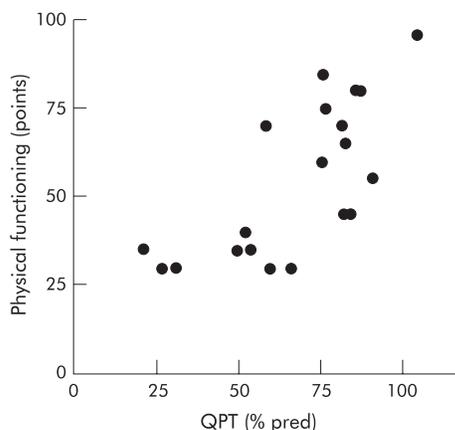


Figure 2 Correlation between muscle force and health status in patients with sarcoidosis. There was a positive correlation between quadriceps peak torque (QPT) and SF-36 scale physical functioning in patients with sarcoidosis. QPT is expressed as percentage predicted (% pred) and physical functioning in arbitrary units (points).

FVC and TLCO which are commonly used to indicate functional impairment in sarcoidosis¹ had weaker or non-significant correlations with these measurements.

Muscle weakness in sarcoidosis

According to the latest statement on sarcoidosis, proximal skeletal muscles weakness is “a common clinical manifestation”.¹ Nevertheless, the present study is the first to observe skeletal muscle weakness in a consecutive sample of patients with sarcoidosis. Our results are in contrast to those of Wirsberger and co-workers who did find respiratory muscle weakness but not skeletal muscle weakness.² This is unlikely to be due to differences in the healthy subjects who were of a similar age (mean 42 years), inspiratory muscle force (mean –115 cm H₂O), and handgrip force (mean 54 kgF for men and 31 kgF for women) to those in the study by Wirsberger

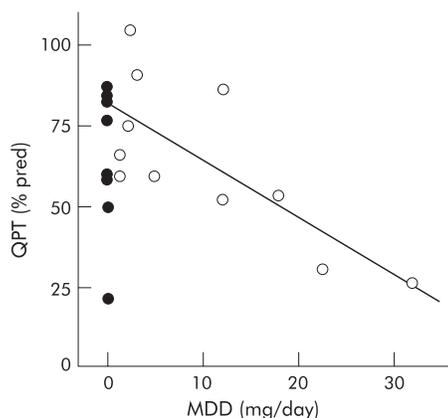


Figure 3 Correlation between mean daily dose of steroids and muscle force in patients with sarcoidosis. There was an inverse correlation between the mean daily dose of methylprednisolone equivalents (MDD) in the 6 month period before testing and quadriceps peak torque (QPT) in patients with sarcoidosis who received oral corticosteroids in the 6 month period before testing (open circles = MDD >0; closed circles = sarcoidosis patients with MDD = 0). MDD is expressed in mg/day and QPT as a percentage predicted (% pred).

Table 4 Characteristics and muscle force in patients taking steroids and those not taking steroids

	Taking steroids	Not taking steroids	Differences between means (95% CI)	p value
BMI (kg/m ²)	26 (4)	29 (6)	3 (-2 to 7)	0.29
FVC (% predicted)	91 (17)	111 (16)	21 (6 to 36)	0.008
FEV ₁ /FVC (%)	79 (3)	74 (11)	-6 (-13 to 2)	0.13
TlCO (% predicted)	75 (16)	80 (14)	6 (-7 to 19)	0.36
Pimax (% predicted)	76 (21)	82 (21)	6 (-13 to 24)	0.52
QPT (% predicted)	64 (24)	69 (20)	5 (-15 to 25)	0.64
6MWD (m)	608 (121)	603 (146)	-5 (-124 to 115)	0.94
Peak VO ₂ (ml/kg/min)	25 (9)	26 (10)	1 (-8 to 9)	0.88

Values are expressed as mean (SD) and as differences between means (with 95% CI).

BMI, body mass index; FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 second; TlCO, carbon monoxide transfer factor; Pimax, maximal inspiratory pressure; QPT, quadriceps peak torque; 6MWD, distance walked in 6 minutes; VO₂, oxygen uptake.

*et al.*⁵ The discrepancy may be explained by differences in the sarcoidosis patients studied. Only about 35% of the patients studied by Wirnsberger *et al* had self-reported complaints of fatigue⁵ while all the patients in our study complained of fatigue. Patients with sarcoidosis who complained of fatigue had more pronounced respiratory muscle weakness,⁵ a lower fat free mass over body weight ratio, and they reported exercise intolerance and muscle pain more frequently than sarcoidosis patients without fatigue.¹⁵ Moreover, in the present study positive correlations of quadriceps peak torque with CRDQ domain fatigue and with SF-36 scale vitality were found in patients with sarcoidosis.

Skeletal muscle weakness in patients with sarcoidosis may be related to corticosteroid treatment. The mean daily dose of oral corticosteroids over the 6 months prior to the study was inversely associated with quadriceps peak torque in the 11 patients with sarcoidosis who received oral corticosteroids during this period (fig 3). Although at first this seems to be straightforward,^{17, 21} this finding is in contrast to several case reports of patients with sarcoidosis in whom normal or improved skeletal muscle function has been reported after treatment with high doses of oral corticosteroids.³⁷⁻³⁹ This clearly shows that the effects of oral corticosteroid treatment on skeletal muscle function in patients with sarcoidosis are equivocal. If sarcoid muscle involvement is present, then steroids may be beneficial. However, steroids may also have a detrimental effect by causing steroid induced myopathy. Future studies to explore the underlying cause of myopathy (corticosteroids, acute myositis, or granulomas) will be of great value for identifying factors that may induce skeletal muscle dysfunction in patients with sarcoidosis. The use of other techniques such as muscle biopsies, electromyography, nerve conduction, and additional blood analyses (such as creatine kinase and electrolytes) should also be considered.⁴⁰

No differences were found in muscle force between patients who took steroids and those who did not (table 4, fig 3). Other factors may therefore contribute to the development of muscle weakness in sarcoidosis. In the present study co-morbidities such as chronic heart failure (no clinical cardiac history) and emaciation (lower limit 95% CI of BMI in patients with sarcoidosis 22.0 kg/m²) can be excluded as possible contributing factors to the generalised muscle weakness in these patients. The positive association between skeletal muscle weakness and the reduced median scores on the SF-36 scale role functioning physical suggests that physical inactivity might play a role in the development of skeletal muscle weakness in sarcoidosis. In fact, complaints of fatigue will probably reduce the day to day physical activities of patients. Consequently, reduced physical activities can induce general deconditioning which, in turn, contributes to increased perceived fatigue and more physical inactivity. Patients may thus end up in a negative vicious circle of deconditioning.

In addition to disuse, circulating levels of proinflammatory cytokines and of IGF-I may be involved in the development of muscle weakness.^{19, 24, 25} Nevertheless, in the present study skeletal and respiratory muscle weakness did not correlate with the circulating levels of IGF-I, IL-6, CXCL8, and TNF- α in patients with sarcoidosis. This may be due to the treatment with oral corticosteroids.⁴¹

Exercise intolerance

Functional and peak exercise capacities were significantly lower than in healthy subjects. Both have been reported before in sarcoidosis and are believed to be limited by the ventilatory and cardiocirculatory systems.⁶⁻¹⁰ The present study is the first to observe a positive correlation between skeletal muscle force and exercise tolerance in patients with sarcoidosis, irrespective of age, sex, height, and body weight. Skeletal muscle dysfunction may therefore contribute to exercise intolerance in sarcoidosis. Higher Borg symptom scores for leg fatigue after the functional and peak exercise test and their inverse relationships with quadriceps peak torque accentuated this. Patients with sarcoidosis in our study tended to have a higher heart rate for the same oxygen uptake (fig S1 online) which suggests physical deconditioning. This is in contrast to the findings of Delobbe and co-workers⁷ who reported lower heart rates in patients with sarcoidosis for similar relative exercise intensities of the achieved peak oxygen uptake compared with healthy subjects. Nevertheless, after expressing their results for oxygen uptake in l/min, Delobbe *et al*⁷ also found higher heart rates for the same oxygen uptake in sarcoidosis patients as in healthy subjects (additional details are available in fig S2 online).

In chronic pulmonary and cardiac diseases skeletal muscle dysfunction significantly contributes to exercise intolerance.^{11, 12} Transcutaneous neuromuscular electrical stimulation^{42, 43} and high intensity resistance training can partially restore these functional deficits.^{44, 45} Subsequent to the presence of skeletal muscle weakness and exercise intolerance, our results provide a clear rationale for investigating the effects of analogous training programmes in sarcoidosis. Besides improving health status, exercise capacity and skeletal muscle function, exercise training may even reduce clinical symptoms of fatigue, anxiety and depression⁴⁶ and lower the circulating levels of TNF- α and its receptors.⁴⁷

Reduced health status

Health status was significantly lower in patients with sarcoidosis than in healthy subjects (table 3). Similar scores on the SF-36 scale have previously been reported in patients with sarcoidosis.⁴ In the present study low SF-36 scores indicated that the physical and social daily activities of the patients were, to a great extent, limited by their perceived physical health or emotional problems, including

accomplishing less than wanted.³¹ The presence of fatigue in daily life was underlined by the difference on the CRDQ domain fatigue between patients with sarcoidosis and healthy subjects, which exceeded the minimal clinically important difference of 2 points used in patients with chronic lung disease.⁴⁸

As shown previously,^{4, 5} several SF-36 scales were associated with FVC, TLCO and with respiratory muscle weakness in patients with sarcoidosis. In the present study, however, the correlations between skeletal muscle weakness, depression, fatigue, and SF-36 scales were clearly stronger.

Methodological and statistical considerations

The mechanisms causing skeletal muscle weakness in patients with sarcoidosis cannot be determined from the present data. Confounding factors (such as corticosteroid treatment, fatigue and physical inactivity) which may have influenced the main outcome (skeletal muscle force) were present in the sarcoidosis patients but not in the healthy subjects. Our control group may not therefore be ideal for determining the mechanisms causing skeletal muscle weakness in sarcoidosis.⁴⁹ Nevertheless, the observation of skeletal muscle weakness in sarcoidosis patients who complain of fatigue is still valid and of clinical relevance.

The research setting and location may have led to biases in the selection of the patients. Sarcoidosis patients with the most severe complaints are more likely to be referred to a tertiary care setting. In addition, only patients who spontaneously report fatigue were included. Patients were all of white ethnic origin while fever, fatigue, and loss of body weight are known to be more frequently present in African-American and Asian Indian patients with sarcoidosis.^{50, 51} The external validity of the study is therefore limited to patients of white ethnic origin with sarcoidosis who complain of fatigue. The findings of the present study need to be reproduced in a larger sample with ethnically diverse patients and with a longer follow up period so that the outcome of clinical care can be assessed.

At the start of the present study (around December 2001) no validated and reliable questionnaire was available to measure fatigue and health status in sarcoidosis. We therefore used the CRDQ domain fatigue and the SF-36, respectively. Recently, however, the Sarcoidosis Health Questionnaire has been validated and appears to be a promising instrument to measure disease specific health status in sarcoidosis.⁵² Significant correlations do not necessarily imply causal relationships. Moreover, statistically significant differences between groups need to be interpreted in the light of the number of comparisons that were made in the present study. Nonetheless, by setting the p value at 0.01, only one out of 100 comparisons was expected to be statistically significant by chance. A priori, no power calculations were performed so non-significant comparisons between the groups may have been caused by a type II error.

Clinical implications

In addition to exercise tests which have been shown to be sensitive physiological measurements to assess the extent of disease in early radiographic stages of sarcoidosis,⁸ the present study underlines the importance of assessing skeletal muscle function in sarcoidosis patients with fatigue. Skeletal muscle force is related to exercise capacity and health status in these patients, and can therefore be seen as an additional measure of their functional status (defined as 'the patient's ability to perform his/her normal level of function in several domains of daily living such as physiologic, psychologic and sociologic performance'⁵³). Hence, muscle force tests, exercise tests, and health status questionnaires provide additional valuable information on patients' functional status and merit

inclusion in the screening and follow up of sarcoidosis patients with fatigue. This is in agreement with DeRemee⁵⁴ who suggested that "the whole patient should be the object of our ministrations, not only pulmonary function or biochemical aberrations".

Physicians have to be aware that patients with sarcoidosis who complain spontaneously of fatigue can have explicit respiratory and skeletal muscle weakness, exercise intolerance, and reduced health status. Moreover, the present results underline again the complexity of sarcoidosis and the need for a multidisciplinary approach in the management of sarcoidosis patients with fatigue.⁵⁵

We conclude that skeletal muscle weakness is present in sarcoidosis patients of white ethnic origin who complain of fatigue. Moreover, this study is the first to show correlations between skeletal muscle weakness, exercise intolerance, and reduced health status in these patients.

ACKNOWLEDGEMENTS

The authors thank physiotherapists D Van Campfort and P Neyrinck for their assistance in gathering the data and for recruiting healthy subjects; physiotherapists I Coosemans and V Barbier for testing all participants; Miss K Maes and Prof Dr G Gayan-Ramirez for handling the plasma samples; Mr W Coopmans for determining circulating levels of IGF-I and IGFBP-3; biostatisticians A Komarek and S Cecere of the Biostatistical Center for their advice; and all the participants who graciously consented to participate in the study.



Additional information is given in the online Appendix and figs S1 and S2 available on the *Thorax* website at www.thoraxjnl.com/supplemental.

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Sources of financial support: 'Fonds voor Wetenschappelijk Onderzoek Vlaanderen' (FWO), Belgium, grant #G.0237.01 and FWO Levenslijn grant #7.0007.00. TT is a FWO postdoctoral fellow.

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Skeletal muscle weakness in patients with sarcoidosis and its relationship with exercise intolerance and reduced health status

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Web-only Appendix

Methods

All measurements took place at the outpatient department of the respiratory rehabilitation division of the University Hospital Gasthuisberg in Leuven, Belgium. Technicians and laboratory workers performing blood analyses and functional tests were unaware of the group-classification of the participants (e.g. sarcoidosis patient or healthy control subject).

Measurements

Venous blood analyses

To minimize possible 'noise' of circadian rhythm (1) and/or of exercise (2) on circulating levels of various cytokines, venous blood was drawn from supine subjects between 08.30 and 09.00 ante meridian, before functional testing. Interleukin (IL)-6 and interleukin-8 (CXCL8) were determined using Human Inflammation Cytometric Bead Array (Becton Dickinson Biosciences, San Diego, CA; range: 1.0 to 625 pg/ml) (3). Tumor necrosis factor-alpha (TNF- α) and its soluble receptors (sTNF-R55 and sTNF-R75) were measured with enzyme-linked immuno assays (EASIA KAC 1752 (range: 5.0 to 130.0 pg/ml), 1762 (range: 0.5 to 47.0 ng/ml) and 1772 (range: 1.7 to 120 ng/ml), respectively, Biosource Europe S.A., Nivelles, Belgium). Insulin-like growth factor-I (IGF-I) was determined using a radio-immuno assay as described previously (4) (range: 45 to 3500 ng/ml). IGF binding protein 3 (IGFBP-3) was assessed using a solid phase immunoradiometric assay (IRMA C.T. BC 1014, Biocade S.A., Liège, Belgium, range: 390 to 7800 ng/ml).

Functional tests

Pulmonary function

Forced expiratory volume in the first second (FEV₁) and forced vital capacity (FVC) were measured according to the European Respiratory Society guidelines for pulmonary function testing (5). In addition, the diffusing capacity for carbon monoxide (TL_{co}) was measured by the single breath method (Sensor Medics 6200, Bilthoven, the Netherlands). Results were expressed as a percentage of the predicted normal values of Quanjer and co-workers (5).

Skeletal muscle force tests

Handgrip force was evaluated using a hydraulic dynamometer (Yamar Preston, Jackson MI). It was assessed at the dominant side with the elbow joint in 90 degrees flexion and the lower arm and wrist in neutral position. Isometric quadriceps peak torque was measured using a Cybex Norm (Enraf-Nonius, Delft, the Netherlands). Peak extension torque was evaluated in sitting position at 60 degrees of knee flexion and 90 degrees of hip flexion. Both tests were performed at least three times, and the best of two reproducible tests was used for analysis. Values were related to reference values of Mathiowetz and co-workers (6) and Decramer and co-workers (7), respectively.

Respiratory muscle force tests

Inspiratory and expiratory muscle strength was measured using a modification of the technique of Black and Hyatt (8). An electronic pressure transducer was used to measure the generated pressure. The signal was recorded for further evaluation. At least five attempts were made to measure expiratory muscle strength from total lung capacity and to measure inspiratory muscle strength from residual volume. Both were determined as the pressure that could be sustained for at least 1 second. Tests were repeated until the variability among the three best attempts was less than 5%. The highest value was expressed as a percent of the predicted value (9).

Functional exercise capacity

Functional exercise performance was measured by a 6-minute walking test. This test was performed in a 53-meter hospital corridor. Encouragement was standardized (10). Transcutaneous oxygen saturation and heart rate were measured during this test. At the end of the test symptom Borg-scores for dyspnea and fatigue were obtained from all participants. The best of two tests was used and expressed as percent of the predicted value (11).

Symptom-limited peak exercise test

Peak exercise capacity was assessed by a maximal incremental cycle exercise test (Partn'air 5400; Medisoft, Dinant, Belgium). After a 2-minute resting period and 3

minutes of unloaded cycling, participants started at 20 watts and cycled until symptom limitation at an incremental workload ($+30 \text{ watt} \cdot 2 \text{ minutes}^{-1}$). Oxygen consumption, carbon dioxide output, and ventilation were measured breath by breath. Heart rate was monitored constantly. At the end of the test symptom Borg-scores for dyspnea and fatigue were obtained from all participants. Peak external work rate and peak oxygen uptake were normalized for height, age and gender (12).

Questionnaires

Health status was measured with the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) (13). It includes eight multiple-item scales that assess physical functioning (the extent to which health limits physical activities such as self-care, walking climbing stairs, bending, lifting, and moderate and vigorous exercise), physical role (the extent to which physical health interferes with work or other daily activities, including accomplishing less than wanted, limitations in the kind of activities, or difficulty in performing activities), pain (the intensity of pain and effect of pain on normal work, both inside and outside home), general health (the personal evaluation of health, including current health, health outlook, and resistance to illness), vitality (feeling energetic and full of pep versus feeling tired and worn out), social functioning (the extent to which physical health or emotional problems interfere with normal social activities), emotional role (the extent to which emotional problems interfere with work or other daily activities, including decreased time spent on activities, accomplishing less, and not working as carefully as usual), and mental health (general mental health, including

depression, anxiety, behavioral-emotional control, general positive effect). Scores can range from 0 (worst) to 100 (optimal).

Participants completed the EQ-5D (formerly the EuroQoL), which provides a simple descriptive profile and a single index value for health status (14). It comprised of 5 dimensions of health: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Moreover, all participants self-rated their health status on a graduated (0-100) visual analogue scale. The Hospital Anxiety and Depression Scale (HADS) was used to assess the presence of clinical symptoms of anxiety and depression (15). Seven questions are related to anxiety and 7 questions are related to depression. Each item is rated on 4-point scale (0 to 3), giving maximum scores of 21 for anxiety and depression, respectively. A score > 10 points is suggestive for the presence of clinical symptoms of anxiety or depression. The domain fatigue of the Chronic Respiratory Disease Questionnaire (CRDQ) was used to assess fatigue (16). It comprised of 4 questions related to fatigue. Each question is rated on a 7-point scale (1 to 7). Scores can range from 4 (worst) to 28 (no fatigue complaints).

Statistical analyses

All statistical procedures were performed using SAS package 6.08 and V8 (SAS Institute, Cary, North Carolina, USA). Data have been tested for normality with the Kolmogorov-Smirnov test. Results are presented as mean (standard deviation) or as median (interquartile range, IQR). A two-tailed unpaired t-test (continuous), a Mann-Whitney U test or a chi square test (binomial) was used to determine differences between sarcoidosis patients and healthy control subjects. Differences between means and their 95% confidence intervals (95% CI) are reported. Moreover, differences

between medians were calculated with bootstrapping technique. Sampling was performed with repeated replacement (5000 replications). The resulting sample of effects then was used to calculate its 95% CI (17). Due to the large number of comparisons a two-sided level of significance was set at $p \leq 0.01$ (18). Pearson product moment correlation (continuous, r) or Spearman rank correlation (r_s) were used to determine the relationship between skeletal muscle force and inflammatory and anabolic markers, and to determine the relationships between physiological factors, exercise capacity and health status in sarcoidosis. *A priori*, a two-sided level of significance was set at $p \leq 0.05$ (18).

Funding source

The funding organization had no involvement in the design of the study; the collection, analysis, and interpretation of the data; and in the decision to approve publication of the finished manuscript.

Reconstruction of original figure of Delobbe and co-workers

Figure S2 of the *web-only appendix* is a reconstruction of the original Figure 2 of Delobbe and co-workers (19). For both groups peak values of peak oxygen uptake were taken (for patients with sarcoidosis: 2.128 liters per minute; for healthy control subjects: 2.909). Afterwards, we calculated the absolute values for oxygen uptake at 0, 10, 20, 30, 40, 50, 60, 70, 80, 90 and 100% of the achieved peak oxygen uptake. Moreover the heart rate values for the respective mean oxygen values were estimated from an enlarged copy of the original Figure 2 (19).

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Legend Figure S1. Heart Rate over Oxygen Uptake in Sarcoidosis and Healthy Subjects.

Mean (standard deviation) heart rate (HR) over mean oxygen uptake (VO_2) in patients with sarcoidosis (\bullet , heart rate = $66 + 54 \cdot \text{oxygen uptake}$) and in healthy subjects (\square , heart rate = $64 + 47 \cdot \text{oxygen uptake}$). Heart rate is expressed in beats per minute (BPM), and oxygen uptake in liters per minute (l/min).

Legend Figure S2. Reconstruction of the Relationship between Heart Rate and Oxygen Uptake.

Mean (standard deviation) heart rate (HR) over mean oxygen uptake (VO_2) in patients with sarcoidosis (\bullet) and in healthy control subjects (\square), reconstructed from values reported by Delobbe and co-workers (19). Heart rate is expressed in beats per minute (BPM), and oxygen uptake in liters per minute (l/min).

Table S1. Circulating Levels of Inflammatory and Anabolic Markers in Sarcoidosis Patients and in Healthy Subjects

	Sarcoidosis		Healthy		Differences between medians (95%CI)	p-value
IL-6, pg·ml ⁻¹	2.40	(1.50-3.70)	2.10	(1.00-4.90)	-0.3 (-1.75 to 1.00)	0.56
CXCL8, pg·ml ⁻¹	3.05	(2.30-4.20)	2.00	(1.70-3.80)	-1.05 (-2.15 to 0.85)	0.29
TNF- α , pg·ml ⁻¹	24.1	(20.2-30.5)	15.3	(12.9-22.5)	-8.8 (-12.6 to -0.91)	0.01
sTNF-R55, ng·ml ⁻¹	1.77	(1.57-2.06)	1.67	(1.59-1.85)	-0.10 (-0.36 to 0.12)	0.31
sTNF-R75, ng·ml ⁻¹	4.34	(3.83-4.95)	3.54	(2.72-4.42)	-0.80 (-1.50 to 0.11)	0.04
IGF-I, ng·ml ⁻¹	138	(125-160)	143	(119-184)	5 (-25 to 40)	0.40
IGFBP-3, ng·ml ⁻¹	2576	(2320-2880)	2644	(2502-2776)	68 (-198 to 284)	0.62

Values are expressed as median (interquartile range) and as differences between medians (95% confidence interval, 95%CI). IL-6=interleukin-6; CXCL8=interleukin-8; TNF- α =tumor necrosis factor-alpha; sTNF-R55=soluble TNF receptor p55; sTNF-R75=soluble TNF receptor p75; IGF-I=insulin-like growth factor-I; IGFBP-3=IGF binding protein 3 (IGFBP-3).

Table S2. Circulating Levels of Inflammatory and Anabolic Markers in Sarcoidosis Patients Taking Steroids and Those Not Taking Steroids

	Taking Steroids		No Steroids		Differences between medians (95%CI)	p-value
IL-6, pg·ml ⁻¹	3.20	(2.40-6.60)	1.80	(1.00-2.40)	-1.4 (-4.8 to -0.4)	0.005
CXCL8, pg·ml ⁻¹	3.20	(2.60-4.40)	2.70	(2.10-4.20)	-0.5 (-2.0 to 1.1)	0.25
TNF- α , pg·ml ⁻¹	22.6	(12.5-24.5)	27.9	(20.6-44.4)	5.3 (-2.8 to 22.8)	0.10
sTNF-R55, ng·ml ⁻¹	1.75	(1.64-2.06)	1.78	(1.50-2.18)	0.03 (-0.39 to 0.43)	0.90
sTNF-R75, ng·ml ⁻¹	4.38	(3.83-4.90)	4.31	(3.62-4.96)	-0.07 (-0.85 to 0.91)	0.74
IGF-I, ng·ml ⁻¹	144	(125-164)	134	(95-157)	-10 (-49 to 29)	0.67
IGFBP-3, ng·ml ⁻¹	2689	(2364-2838)	2446	(2125-2922)	-244 (-592 to 309)	0.57

Values are expressed as median (interquartile range) and as differences between medians (95% confidence interval, 95%CI). IL-6=interleukin-6; CXCL8=interleukin-8; TNF- α =tumor necrosis factor-alpha; sTNF-R55=soluble TNF receptor p55; sTNF-R75=soluble TNF receptor p75; IGF-I=insulin-like growth factor-I; IGFBP-3=IGF binding protein 3 (IGFBP-3).

Table S3. Scores on Questionnaires in Sarcoidosis Patients Taking Steroids and Those Not Taking Steroids

	Taking Steroids	No Steroids	Differences between medians (95% CI)	p-value
SF-36 (0 to 100)				
Physical functioning	35 (30-60)	67.5 (45-75)	32.5 (-10 to 42.5)	0.07
Role functioning physical	0 (0-50)	12.5 (0-50)	12.5 (-37.5 to 50)	0.51
Bodily pain	40 (40-50)	55 (50-70)	15 (-5 to 30)	0.16
General health	30 (20-60)	45 (20-60)	15 (-15 to 40)	0.55
Vitality	45 (20-65)	40 (30-60)	-5 (-30 to 25)	0.81
Social functioning	63 (38-88)	69 (50-88)	6 (-37.5 to 37.5)	0.95
Role functioning emotional	100 (0-100)	100 (67-100)	0 (-33.3 to 100)	0.72
Mental health	72 (44-80)	60 (44-80)	-12 (-36 to 22)	0.50
HADS (0 to 21)				
Anxiety	6 (2-9)	9 (6-11)	3 (-1 to 7)	0.14
Depression	8 (3-13)	7 (3-11)	-1 (-8 to 6)	0.50

Table S3. Scores on Questionnaires in Sarcoidosis Patients Taking Steroids and Those Not Taking Steroids, continued

Values are expressed as median (interquartile range) and as differences between medians (95% confidence interval). Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) included 8 multiple-item scales. Hospital Anxiety and Depression Scale (HADS) included 7 questions related to anxiety and 7 questions are related to depression.

Table S4. Correlations between Questionnaires and Muscle Force in Sarcoidosis**Patients**

	QPT	Depression	Fatigue
SF-36			
Physical functioning	0.70	-0.67	0.57 [§]
Role functioning physical	0.59 [§]	-0.54 [§]	0.67
Bodily pain	0.62 [§]	-0.68	0.62 [§]
General health	0.31	-0.42 [*]	0.78
Vitality	0.44 [†]	-0.77	0.78
Social functioning	0.50 [‡]	-0.82	0.57 [§]
Role functioning emotional	0.30	-0.61 [§]	0.74
Mental health	0.56 [§]	-0.76	0.89

Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36, expressed in arbitrary units, points), quadriceps peak torque (QPT, expressed as a percent of the predicted value), depression measured with Hospital Anxiety and Depression Scale, and CRDQ-domain fatigue (both expressed in arbitrary units, points). *

^{*} p=0.06, [†] p=0.05, [‡] p=0.02, [§] p=0.01, ^{||} p<0.001

