

BODY COMPOSITION PROFILING IN A DUTCH SARCOIDOSIS POPULATION

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ABSTRACT. *Background:* Muscle atrophy is a common problem in many chronic inflammatory diseases. It may occur as part of a generalized wasting process (cachexia) or be hidden due to preservation of fat mass (sarcopenia, sarcopenic obesity). *Objectives:* The aim of this study was to assess the prevalence of cachexia and muscle atrophy in sarcoidosis and their association with disease activity and severity. *Methods:* A cross-sectional study was performed in 423 sarcoidosis patients. Fat-free mass was assessed as an indirect measure of muscle mass by bioelectrical impedance analysis. Patients were stratified based on body mass index (BMI) and fat-free mass index (FFMI). Muscle atrophy was defined as FFMI <15 kg/m² for women and <17 kg/m² for men corresponding to <10th percentile of current reference values; cachexia as BMI <20 combined with muscle atrophy. Multivariate linear regression models were used to adjust for potential confounders. *Results:* Of the patients examined, 58% were categorized as overweight (37%) or obese (21%), whereas 7% were underweight. Muscle atrophy was present in 25% and cachexia in 5%. Patients with muscle atrophy showed significantly worse lung function (DLCO, FEV₁, FVC, all p-values <0.01) and impaired exercise capacity (VO₂max, p<0.001). The associations were most pronounced in patients with cachexia. Associations remained significant after adjustment for potential confounders. *Conclusions:* Muscle atrophy was present in 25% of sarcoidosis patients and was associated with more severe pulmonary disease. Prospective studies with longitudinal design are needed to assess the association between muscle atrophy and disease severity in sarcoidosis. (*Sarcoidosis Vasc Diffuse Lung Dis* 2013; 30: 289-299)

KEY WORDS: Sarcoidosis; Body composition; Muscle atrophy; Cachexia; Lung function; Exercise capacity.

INTRODUCTION

Sarcoidosis is a multisystemic disease characterized by inflammatory activity with formation of noncaseating granulomas in various organ systems (1, 2). The etiology is unknown, but immunological, genetic and environmental factors and oxidative stress appear to play a role (2-4). The lungs are most commonly affected, but in 50% of cases extrapul-

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monary sites can be involved as well (5). In severe sarcoidosis, the release of inflammatory mediators causes derangement of organ physiology and finally functional impairment and related symptoms. The disease stabilizes or improves in many cases over the first two years, but may worsen and become chronic in others (1).

Since practically every organ can be involved, patients may present with a wide variety of clinical signs and symptoms (1, 2). In addition, patients can also suffer from generic disease symptoms, such as fatigue and exercise intolerance, with substantial impact on the quality of life of patients and their families (1, 6-14). An important determinant of these symptoms in other chronic inflammatory diseases (e.g. chronic obstructive pulmonary disease (COPD) and rheumatoid arthritis (RA)) is skeletal muscle weakness resulting from muscle atrophy (15-20), but a detailed profile of body composition in relation to physical functioning is not yet available for sarcoidosis.

Muscle atrophy may occur as part of a generalized wasting process (cachexia) or be hidden due to preservation of fat mass (often referred to as sarcopenia, sarcopenic obesity). According to a recent consensus statement, cachexia is defined as a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle mass with or without loss of fat mass, with the prominent clinical feature of weight loss of at least 5% during the previous 12 months or a body mass index (BMI) <20 kg/m² (21). While the disease burden of cachexia is well established, the exact cause and underlying mechanisms of muscle atrophy are still poorly understood, but are likely to be multifactorial (17). Putative triggers of muscle wasting are inflammation, oxidative stress, hypoxemia, inactivity, ageing, smoking and endogenous or exogenous glucocorticosteroids (GC) (17, 20, 22, 23). In contrast to other chronic lung diseases, smoking is not a cause of sarcoidosis, and is even associated with disease protection (24, 25). Moreover, a low prevalence of smoking is observed among sarcoidosis patients (25). Other possible triggers may converge during the clinical course of sarcoidosis. It is especially since inflammation is the most important characteristic of sarcoidosis, with oxidative stress being one of the etiological factors and GC being the first-line treatment option, that considerable impact on muscle mass status is

highly likely (1, 2). Moreover, hypoxemia and inactivity have been found to be problems in severe sarcoidosis as well (11, 26). Sarcoidosis patients are relatively young, so the contribution of age-associated muscle mass loss is small (1, 5).

The aim of this study was to investigate the prevalence of different body composition profiles in patients with sarcoidosis and to assess the association of muscle atrophy and cachexia with disease activity and severity.

METHODS

Patients

A cross-sectional study was performed among 423 consecutive chronic refractory Caucasian sarcoidosis patients who were referred to the former ild (interstitial lung disease) care team, a tertiary referral centre of the Department of Respiratory Medicine of the Maastricht University Medical Centre+ (MUMC+), between 1 January 2004 and 31 December 2009. The diagnosis of sarcoidosis was based on consistent clinical features and bronchoalveolar lavage fluid analysis, according to the guidelines of the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) (1), with biopsy-proven noncaseating epithelioid cell granulomas confirming sarcoidosis in 74%. Other causes of granulomatous disease were excluded. Six of the patients suffered from GC induced diabetes. None of the other patients had relevant medical history or comorbidity. All investigations used in this study were performed during the first visit to the outpatient clinic of the referral centre, and the questionnaire was completed the same day. Other relevant clinical data were obtained from medical records. The study was approved by the Medical Ethics Board of the MUMC+ (METC 11-4-116) and all participants gave their written informed consent.

Body composition

Body height was measured to the nearest 0.5 cm while the subjects were standing and barefoot. Body weight was measured with the patients wearing indoor clothing and without shoes on a calibrated beam scale to the nearest 0.1 kg (model 708; Seca,

Hamburg, Germany). Body weight was adjusted for body height by calculating the BMI as weight (kg)/height (m)².

Fat-free mass (FFM) was assessed as an indirect measure of muscle mass by single-frequency bioelectrical impedance analysis (BIA; RJL Systems, Detroit, MI, USA) in the supine position with arms and legs abducted and not touching the body (27). Patients were in non-fasting condition, but at least 2 hours after their last meal. FFM was calculated from height²/resistance and body weight using the Lukaski formula (28). In order to assess the degree of functional tissue depletion, FFM was adjusted for body size by calculating the FFM index (FFMI, FFM/height² (kg.m⁻²)) (27). BIA has been extensively validated in COPD and other chronic wasting conditions. FFM correlated well with deuterium dilution as a reference technique (29).

Muscle atrophy was defined as FFMI <15 kg/m² for women and <17 kg/m² for men corresponding to <10th percentile of current reference values established in a large Caucasian group of healthy subjects (30). Patients were stratified based on BMI and FFMI into six defined categories: cachexia, defined as BMI <20 combined with muscle atrophy according to the definition proposed by Evans et al. (21); underweight, defined as BMI <20 combined with normal muscle mass; hidden muscle atrophy, defined as BMI 20–<25 combined with muscle atrophy; normal body composition, defined as BMI 20–<25 combined with normal muscle mass; overweight, defined as BMI 25–<30; and obesity, defined as BMI ≥30.

Questionnaire

Fatigue was measured with the 10-item fatigue assessment scale (FAS), which indicates both physical and psychological fatigue. Each item has a five-point rating scale, and FAS scores range from 10 to 50. FAS scores <22 indicate non-fatigued persons, scores of 22–34 indicate fatigued persons and scores of ≥35 indicate extremely fatigued persons (31). The psychometric properties of the FAS have been found to be good in sarcoidosis (31, 32).

Chest radiography

The chest radiographs were scored by an experienced thoracic radiologist, blinded to the patient's

clinical history. Chest X-ray radiographic abnormalities were classified according to the Scadding radiographic staging system (1). Five stages of radiographic abnormality were distinguished: stage 0 (normal chest X-ray), stage I (bilateral hilar lymphadenopathy (BHL)), stage II (BHL and parenchymal abnormalities), stage III (parenchymal abnormalities without BHL) and stage IV (end-stage lung fibrosis).

Laboratory tests

The inflammatory markers angiotensin-converting enzyme (ACE), soluble-interleukin2-receptor (sIL2R) and C-reactive protein (CRP) were used to assess sarcoidosis inflammatory activity (33–36). Serum ACE was measured by a colorimetric method (cat. no. FU 116; Fujirebio Inc.) (33). Serum levels of sIL2R were determined using an IMMULITE Automated Analyzer (33). The CRP concentration was measured by a turbidimetric method on a SYNCHRON LX (Beckman Coulter Inc., Fullerton, CA, USA) (33).

Pulmonary function

The diffusing capacity for carbon monoxide (DLCO) was measured using the single-breath method (Masterlab, Jaeger, Würzburg, Germany). Forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) were measured with a pneumotachograph (Masterlab, Jaeger, Würzburg, Germany) (37). Pulmonary function tests were performed according to the standards of the European Community of Coal and Steel (37). Values were expressed as a percentage of predicted values.

Exercise capacity and muscle strength

Patients performed a symptom-limited incremental maximal exercise test (10 W min⁻¹) on an electronically braked cycle ergometer (Cornival 400; Lode, Groningen, The Netherlands) from which maximal oxygen uptake (VO₂max) was determined (26). This exercise test was performed according to the American Thoracic Society's standards (38). The six-minute walk distance (6MWD) was used to assess functional exercise capacity and was performed according to the American Thoracic Society guide-

lines (11, 13, 39–41). Values were expressed as a percentage of predicted values.

A global impression of muscle strength was obtained by measuring the maximal isometric handgrip force (HGF) of the dominant hand (in kilograms) with the Jamar dynamometer (Jamar, Sammons Preston, Chicago, USA), which is a valid and reliable instrument (42, 43). Maximal inspiratory pressure (PI,max) was assessed by measuring maximal respiratory mouth pressures using the method of Black and Hyatt (44). All tests were performed as reported previously (11).

Statistical analysis

Results are presented as means (\pm SD) for normally distributed continuous variables and as frequencies and percentages for nominal or ordinal variables. The distribution of characteristics and outcome measures of patients with and without muscle atrophy were compared using the Student's t-test or one-way ANOVA test for normally distributed continuous variables and the non-parametric tests Mann-Whitney U or Kruskal-Wallis H for non-normally distributed variables. Pearson's Chi-squared test was used to assess differences in nominal and ordinal variables. Multivariate linear regression models were used to ad-

just for potential confounders. A p-value ≤ 0.05 was considered to represent a statistically significant relationship. SPSS-pc version 16.0 (SPSS Inc., Chicago, Illinois, USA) was used for analysis.

RESULTS

Patient characteristics are summarized in Table 1. Twenty-five percent (107/423) of the patients examined showed muscle atrophy. The time since diagnosis varied from 6 months to 37 years prior to the first visit, with a mean value of 4.3 (± 5.8) and a median of 2.0 years. The mean age of the total study group was 43 (± 11) years, 46% were female and 10.6% smoked. Fifty-three percent of patients were on pharmacological treatment during data collection: 153 patients used prednisone alone (dose 2.5–60 mg daily, mean dose 11 mg daily); 15 patients methotrexate (MTX) alone (dose 5–15 mg weekly, mean dose 9.0 mg weekly); 29 patients the combination of prednisone (5–30 mg daily, mean dose 13 mg daily) plus MTX (2.5–15 mg weekly, mean dose 10 mg weekly); and 21 patients were on anti-tumor necrosis factor-alpha (TNF- α) treatment with or without other therapeutics (prednisone or MTX). In patients with muscle atrophy, the presence of ex-

Table 1. Summary of patient characteristics.

Variable	Muscle atrophy (FFMI <15f/17m)	Normal muscle mass (FFMI \geq 15f/17m)	Total
Demographics			
Number of patients (%)	107 (25.3%)	316 (74.7%)	423 (100%)
Female/male (%)§	45.3/54.7	47.7/52.3	45.9/54.1
Age (y)‡	41.7 \pm 12.0	43.9 \pm 10.8	43.3 \pm 11.1
Time since diagnosis (y)‡	4.5 \pm 5.4	4.2 \pm 6.0	4.3 \pm 5.8
Smoking (%)§	11.2	10.4	10.6
Extrathoracic involvement (%)§	75 (70.1%)	238 (75.3%)	313 (74.0%)
Body composition			
BMI (kg/m ²)‡	23.1 \pm 3.6*	27.7 \pm 5.0	26.6 \pm 5.1
- Female/male‡	23.6 \pm 3.7/22.6 \pm 3.4	28.0 \pm 5.8/27.5 \pm 4.1	26.9 \pm 5.7/26.3 \pm 4.5
FFMI (kg/m ²)‡	14.9 \pm 1.3*	18.3 \pm 2.0	17.4 \pm 2.3
- Female/male‡	14.0 \pm 0.9/15.8 \pm 1.0†	17.0 \pm 1.4/19.4 \pm 1.6†	16.2 \pm 1.9/18.5 \pm 2.2†
Pharmacological treatment (%)§			
Prednisone use (%)§	56.1	52.5	53.4
Methotrexate use (%)§	48.6	46.5	47.0
Anti-TNF- α use (%)§	12.1	13.3	13
	6.5	4.4	5.0

*Significant difference between the muscle atrophy and normal muscle mass groups, $p < 0.05$; †Significant difference between women and men, $p < 0.001$; ‡All values are expressed as mean \pm SD and were tested with one-way ANOVA; §All values are expressed as frequencies and/or percentages and were tested with Pearson's Chi-squared test; BMI, body mass index; f, female; FFMI, fat-free mass index; m, male; TNF- α , tumor necrosis factor-alpha; y, years.

trathoracic sarcoidosis involvement did not differ significantly from patients with normal muscle mass.

The mean BMI was 26.6 (± 2.1) kg/m², indicating some excess weight. No significant difference was found between men and women. Mean FFMI was 17.4 (± 2.3) kg/m² for the total group and was, as expected, significantly lower in women compared to men ($p < 0.001$); both could, however, be categorized as normal. Apart from BMI and FFMI, patient characteristics did not differ between the muscle atrophy and normal muscle mass groups.

Figure 1 shows an overview of the prevalence of the different body composition profiles. Fifty-eight percent of the patients examined were categorized as overweight (37%) or obese (21%), whereas 7% showed a BMI below normal and 35% a normal BMI. Of the 107 patients with muscle atrophy, 22 (20%) were overweight or obese, whereas 21 (20%) had a BMI <20 (cachexia, 5% of the total population). The majority ($n=64$, 60%) of patients with muscle atrophy were found to have a normal BMI (hidden muscle atrophy, 15% of the total population). A total of 82 patients (19%) had a completely normal body composition (normal BMI and normal FFMI).

Table 2 presents disease parameters for patients with and without muscle atrophy. Fatigue, assessed by the FAS, did not differ between the two groups. The distribution of chest X-ray stages was significantly different in the two groups ($p=0.024$), with chest X-ray stage IV being more prevalent in muscle

atrophic patients (34%) compared to chest X-ray stages 0–III (24%). Despite a clear tendency towards higher values of sIL2R in muscle atrophy, sIL2R did not differ significantly between the two groups. This was also true for a subgroup of untreated patients, for whom no difference in sIL2R could be established between the two muscle mass groups (data not shown). The levels of sIL2R were not normally distributed and the range was wide (160–9684 U/mL). The mean values of the other inflammatory parameters ACE and CRP were similar in both groups. The muscle atrophic patients had significantly lower values on lung function test results (DLCO $p < 0.001$, FEV1 $p=0.005$, FVC $p < 0.001$) and for exercise capacity (VO₂max $p < 0.001$). A tendency towards lower values of 6MWD, expressed as a percentage of predicted value, was observed in the patients with muscle atrophy, but this tendency did not reach significance ($p=0.165$). The muscle strength parameters PI_{max} and HGF of the dominant hand did not differ significantly between the two muscle mass groups, despite a tendency towards lower values of both tests in the muscle atrophy group.

Table 3 shows the between-group differences in mean values of lung function and exercise capacity parameters, with 95% confidence intervals, before and after adjustment for potential confounders such as gender, age, time since diagnosis, pharmacological treatment status and smoking, based on multivariate regression models. After adjustment, the differences between the groups with and without muscle atrophy remained statistically significant.

Since muscle atrophy was associated with significantly worse disease characteristics, and since it was especially frequent in patients with BMI <25, an additional analysis was performed to investigate a potential difference in risk profile between the cachectic subgroup and the hidden muscle atrophy group. Patients with cachexia demonstrated significantly more impaired lung function and VO₂max test results compared to hidden muscle atrophic patients ($P < 0.05$), as depicted in Figure 2. Furthermore, significantly higher values of ACE were detected in patients with cachexia, whereas the other inflammatory parameters were similar for both groups (data not shown).

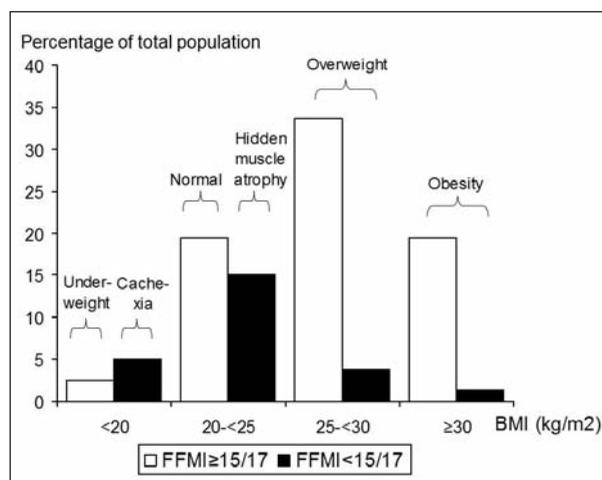


Fig. 1. Body composition profiles in a sarcoidosis sample. Stratification of FFMI according to <10th percentile of current reference values established in a large Caucasian group of healthy subjects (30); BMI, body mass index; FFMI, fat-free mass index.

DISCUSSION

Table 2. Distribution of disease parameters for groups of sarcoidosis patients with and without muscle atrophy.

Variable	Muscle atrophy (FFMI <15f/17m)	Normal muscle mass (FFMI ≥15f/17m)	Total	p-value
Number of patients (%)	107 (25.3%)	316 (74.7%)	423 (100%)	-
FAS score† n	31.1 ±7.1 97	29.9 ±9.0 295	30.2 ±8.5 392	0.229
Chest X-ray stage 0/I/II/III/IV (%)‡	49.5/2.8/20.6/6.5/20.6*	41.5/9.8/22.8/12.3/13.6	43.5/8.0/22.2/10.9/15.4	0.024
Inflammatory markers				
-ACE (U/L)† n	23.2 ±16.0 105	22.0 ±11.0 314	22.3 ±12.4 419	0.410
-sIL2R (U/mL)§ n	1852 ±2297 86	1391 ±1613 237	1514 ±1828 323	0.440
-CRP (mg/L)§ n	8.4 ±8.3 107	10.5 ±18.8 313	10.0 ±16.8 420	0.617
Lung function				
-DLCO (% of predicted)† n	76.5 ±19.1* 107	83.6 ±16.8 313	81.8 ±17.7 420	<0.001
-FEV1 (% of predicted)† n	83.3 ±24.9* 106	90.3 ±21.3 312	88.5 ±22.4 418	0.005
-FVC (% of predicted)† n	92.0 ±21.8* 106	99.9 ±19.2 313	97.9 ±20.1 419	<0.001
Exercise capacity				
-VO ₂ max (% of predicted)† n	62.3 ±19.7* 42	81.6 ±23.7 136	77.0 ±24.2 178	<0.001
-6MWD (% of predicted)† n	64.5 ±16.2 51	68.0 ±14.9 140	67.1 ±15.3 191	0.165
Muscle strength				
-HGF dominant hand (% of predicted)† n	87.5 ±16.7 23	94.9 ±25.9 90	93.4 ±24.4 113	0.193
-PI ₁ max (% of predicted)† n	84.6 ±26.0 100	87.9 ±30.1 293	87.0 ±29.1 393	0.193

*Significant difference between the muscle atrophy and normal muscle mass groups, $p < 0.05$; †All values are expressed as mean ±SD and were tested with one-way ANOVA; ‡All values are expressed as frequencies and/or percentages and were tested with Pearson's Chi-squared test; §All values are expressed as mean ±SD and were tested with Mann-Whitney U test; 6MWD, 6 minute walk distance (13, 40, 41); ACE, angiotensin-converting enzyme; CRP, C-reactive protein; DLCO, diffusing capacity for carbon monoxide (37); f, female; FAS, fatigue assessment scale (31); FEV1, forced expiratory volume in 1 s (37); FFMI, fat-free mass index; FVC, forced vital capacity (37); HGF, handgrip force (42, 43); m, male; PI₁max, maximal inspiratory pressure (11, 44); sIL2R, soluble-IL2-receptor; VO₂max, maximal oxygen uptake (26, 38).

This is the first study to demonstrate that muscle atrophy is a substantial problem in sarcoidosis. In our sample of patients with sarcoidosis - a large Dutch cohort - 25% had muscle atrophy, defined as FFMI <15 for women and <17 for men. Five percent of patients had cachexia, defined as BMI <20 combined with the presence of muscle atrophy. Muscle atrophy in sarcoidosis was associated with worse lung function and more impaired exercise capacity (as indicated by VO₂max). These associations were

strongest in patients with cachexia.

Sarcoidosis is an intriguing inflammatory disease (2). Sarcoidosis patients tend to be relatively young, non-smokers and have only mild or no comorbidity potentially affecting or aggravating muscle atrophy (1, 5). Furthermore, the presence of extrathoracic sarcoidosis involvement did not differ between the two muscle mass groups. Nevertheless, we found muscle atrophy in sarcoidosis to be clearly more common (25%) than in a study of a large

Table 3. Differences in mean values of lung function and exercise capacity parameters with 95% confidence intervals, before and after adjustment for potential confounders, between patients with FFMI <15/17 and patients with FFMI ≥15/17†.

	Univariate				Multivariate			
	b	p-value	95% CI of b		b	p-value	95% CI of b	
			Lower	Upper			Lower	Upper
DLCO%								
FFMI <15/17 vs. ≥15/17	-7.074	<0.001*	-10.912	-3.235	-6.695	0.001*	-10.473	-2.916
FEV1%								
FFMI	-7.021	0.005*	-11.935	-2.107	-6.425	0.007*	-11.057	-1,792
FVC%								
FFMI	-7.841	<0.001*	-12.230	-3.452	-6.967	0.001*	-11.098	-2.835
VO ₂ max%								
FFMI	-19.242	<0.001*	-27.204	-11.279	-17.155	<0.001*	-24.241	-10.069

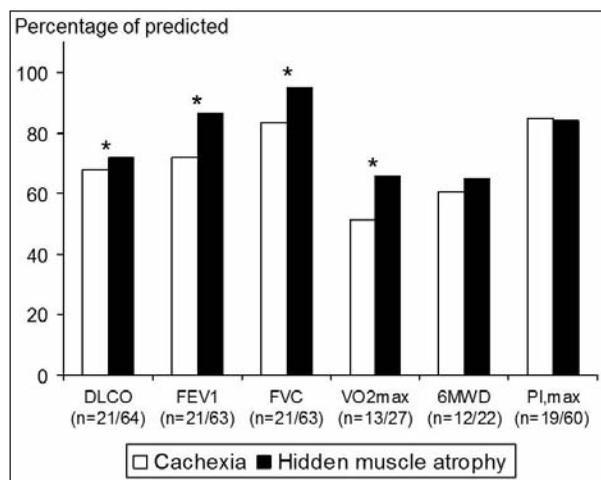
* $p < 0.05$; †Results from multivariate linear regression models, with adjustment for gender, age, time since diagnosis, pharmacological treatment status and smoking; b, unstandardized regression coefficient; DLCO%, diffusing capacity for carbon monoxide, percentage of predicted (37); FEV1%, forced expiratory volume in 1 s, percentage of predicted (37); FVC%, forced vital capacity, percentage of predicted (37); VO₂max%, maximal oxygen uptake, percentage of predicted (26, 38).

healthy Caucasian European population aged 35–54 years (10%), which used the same defining criteria as those used in our study (30). On the other hand, the prevalence was in agreement with studies showing muscle atrophy percentages of 18–26% in COPD (15, 45) and of 20% in RA (18). In more severe

stages of COPD, percentages of muscle atrophy up to 36–40% have been found (16, 46). In line with this, we found muscle atrophy in 34% of the more severe pulmonary sarcoidosis patients with chest X-ray stage IV and more severe respiratory functional impairment (RFI).

Muscle atrophy was associated with significantly impaired lung function and cardiopulmonary exercise test results, expressed as VO₂max, which is in agreement with findings in COPD (15, 16). However, muscle strength and 6MWD only showed a non-significant trend towards lower values in muscle atrophy. The inclusion of leg muscle measurements, besides PI_{max} and HGF, would be preferable to assess muscle strength. Marcellis et al. found a trend towards lower levels of FFMI in sarcoidosis patients with reduced leg muscle strength (11). Another explanation for the non-significant association between muscle mass and strength may be the negative effect of systemic GC treatment on muscle strength (47, 48). Moreover, studies in patients with COPD have clearly established that the 6MWD is not only determined by muscle mass, but also by RFI, fatigue and muscle strength (11, 13, 49, 50).

Fatigue in sarcoidosis has a complex and multifaceted etiology, with systemic inflammation, clinical and psychological factors playing a role (27, 51, 52). Some studies found that patients with peripheral muscle strength impairment were more fatigued

**Fig. 2.** Mean lung function, exercise capacity and muscle strength parameters in cachexia and hidden muscle atrophy.

* $p < 0.05$ (one-way ANOVA); cachexia, BMI <20 and FFMI <15 (f) or <17 (m); hidden muscle atrophy, BMI 20–<25 and FFMI <15 (f) or <17 (m); 6MWD, 6 minute walk distance (13, 40, 41); DLCO, diffusing capacity for carbon monoxide (37); f, female; FEV1, forced expiratory volume in 1 s (37); FVC, forced vital capacity (37); m, male; VO₂max, maximal oxygen uptake (26, 38); PI_{max}, maximal inspiratory pressure (11, 44).

than patients with normal muscle strength (11, 53). The present study showed that fatigue, assessed by the FAS, did not differ between groups stratified according to muscle mass status. However, examining the association between fatigue and muscle mass is difficult, since BIA is only capable of assessing overall FFM, instead of distinguishing appendicular FFM. Furthermore, the FAS examines a subjectively experienced level of fatigue. Studies in patients with COPD have used a more objective tool for the assessment of leg muscle fatigue, by measure electrical activity of the quadriceps, and found that muscle fatigue was linked to the oxidative capacity of the muscle rather than to muscle mass (54, 55). An important role for oxidative stress and antioxidant capacity in the disease genesis has also been demonstrated in sarcoidosis (3, 56). Future research into muscle fatigue is warranted to assess the influence of other possible etiological factors, such as decreased oxidative muscle capacity.

The prevalence of cachexia in our study was found to be 5%. Of the more severe pulmonary sarcoidosis patients with chest X-ray stage IV and more RFI, 14% had cachexia. In COPD, cachexia is described to occur in 11–28% of patients (16, 45, 46). Many COPD studies were performed in older patient populations with advanced stages of COPD, who had relevant comorbidities and smoking history, whereas the relatively young patient population with sarcoidosis has little or no comorbidity. This might at least partly explain the higher prevalence found in COPD. Just as in COPD (17, 57), an increased whole body protein turnover in sarcoidosis is associated with increased resting energy expenditure (REE), leading to an energy imbalance enhancing cachexia (27). This effect might explain the high prevalence of cachexia in advanced sarcoidosis cases with chest X-ray stage IV.

Cachectic patients in our study showed more impaired lung function and VO_2max compared to those with hidden muscle atrophy. Since cachectic patients are characterized not only by muscle atrophy but also by a low BMI, physicians are more likely to be alarmed, whereas patients with hidden muscle atrophy are less likely to be noticed based on their physical appearance. Nevertheless, these patients also had worse lung function and VO_2max , although to a lesser extent than cachectic patients. Since the proportion of patients with hidden muscle atrophy is

large, it is important for physicians to be aware of this (see Figure 3).

The use of exogenous GC, the most frequently used pharmacological therapeutic option in sarcoidosis, can induce an iatrogenic hypercortisolemic state, contributing to muscle wasting (58). Hypercortisolemia, the result of endogenous GC production and consistent with stress during illness including sarcoidosis, represents a persistent catabolic stimulus leading to reduced protein synthesis and increased loss of muscle mass (59). This seems, however, to be a less important factor in sarcoidosis, since decreased baseline adrenocorticotrophic hormone (ACTH)/cortisol levels as a consequence of the sar-

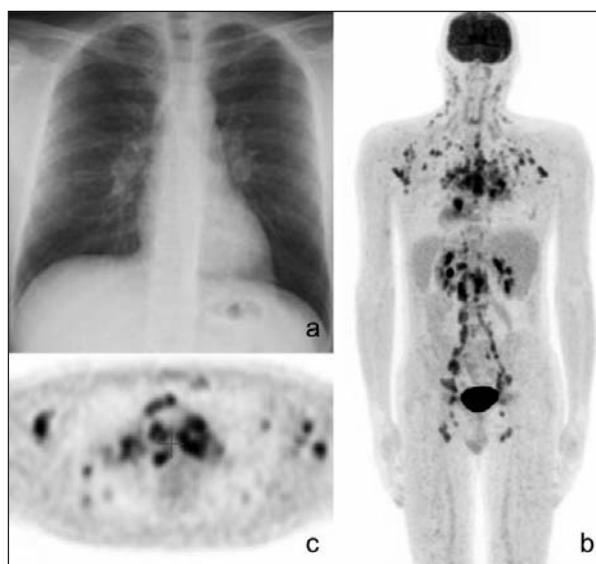


Fig. 3. Example of a sarcoidosis patient with hidden muscle atrophy.

A 32-year-old man with a history of sarcoidosis of 5 years has a BMI of $21.9 \text{ kg}\cdot\text{m}^{-2}$ and a FFMI of $14.9 \text{ kg}\cdot\text{m}^{-2}$, indicating hidden muscle atrophy. ACE is 27 U/L , sIL2R 5053 U/mL and CRP 11 mg/L ; elevated sIL2R indicating inflammatory activity. DLCO is 69%, FEV1 52% and FVC 62% of predicted, indicating severe respiratory functional impairment. Chest X-ray, however, shows only mild abnormalities consisting of bilateral hilar lymphadenopathy without parenchymal involvement (stage I) (a). PET image of the total body shows inflammatory activity indicated by increased FDG uptake in multiple lymph nodes and to a lesser extent in pulmonary parenchyma bilaterally (b). PET image at thoracic level shows mildly increased FDG uptake in the pulmonary parenchyma bilaterally and extensive uptake in axillary and mediastinal lymph nodes (c). ACE, angiotensin converting enzyme; BMI, body mass index; CRP, C-reactive protein; DLCO, diffusing capacity for carbon monoxide (37); ^{18}F FDG, fluorine-18-fluorodeoxyglucose; FEV1, forced expiratory volume in 1 s (37); FFMI, fat-free mass index; FVC, forced vital capacity (37); PET, ^{18}F -FDG positron emission tomography/computed tomography; sIL2R, soluble-IL2-receptor.

coidosis itself have been demonstrated (60). An inappropriate low response to exercise-associated interleukin-6 (IL-6) increase has also been found, reflecting either a dysfunctional IL-6-induced stimulation of the hypothalamic–pituitary–adrenal axis or an adaptation of this axis to the chronically elevated IL-6 concentrations in sarcoidosis (61).

The exact mechanism underlying the transition from flares of inflammation to muscle atrophy remains unresolved (62). In both COPD and sarcoidosis, a systemic inflammatory response, reflected by elevated levels of TNF- α , presumably contributes to muscle wasting (63, 64). Our study, however, found similar degrees of inflammation for both muscle mass groups. The cachectic patients had significantly higher values of ACE compared to the hidden muscle atrophic patients, whereas sIL2R and CRP were similar. The up-regulation of transient systemic inflammation may only appear during acute flares of disease activity, as has been shown for acute exacerbations in COPD (62, 65). Muscle nuclear factor-kappaB (NF- κ B) activation is thought to play a role as well (62). It is likely that flares of systemic inflammatory activity associated with NF- κ B activation also contribute to muscle wasting in sarcoidosis (3, 27, 66, 67). Moreover, as the inflammatory markers were measured in different conditions in terms of disease duration and activity, an association between inflammation and muscle atrophy may have been missed. Furthermore, the inflammatory capacity of visceral fat is considerably greater than that of subcutaneous fat (68, 69). Since in sarcopenic obesity, visceral fat increases while subcutaneous fat declines, the contribution of fat-associated inflammatory activity can be expected especially in advanced age groups (68, 69). Since BIA is not able to establish the precise bodily distribution of fat mass, we could not control for fat mass localization as a possible influencer of systemic inflammation.

Limitations of the study

A limitation of this cross-sectional study was that patients were included at different time points after diagnosis, so disease conditions varied at inclusion. Furthermore, our study involved a first attempt to assess body composition profiles in sarcoidosis. FFM was assessed as an indirect measure of muscle mass by BIA, a suitable and easy to perform screening instrument. It has been recommended, however, to use a combination

of more reliable (deuterium dilution) or specific measuring techniques such as dual energy X-ray absorptiometry (DEXA), magnetic resonance imaging (MRI) or computerized tomography (CT) for more extensive analysis in patients at high risk for muscle atrophy (70–73). Since DEXA, MRI and CT provide regional assessment of three or even four compartments, it can establish the bodily distribution of muscle and fat mass in more detail, which is not possible by BIA assessment (71–73).

Directions for future studies

Prospective longitudinal follow-up studies with uniform measuring conditions at diagnosis and during the course of the disease will be necessary to assess the relations between body composition and systemic inflammation and disease severity in sarcoidosis. A useful approach would be to examine the value of screening for malnutrition using questionnaires, in order to select patients at high risk for muscle atrophy. Another interesting topic of research could be to investigate the effect of pharmacological anti-inflammatory therapeutics on body composition. In addition, the effect on muscle maintenance of a multidisciplinary rehabilitation program, consisting of dietary intervention combined with physical training, needs to be established, along with the potentially different responses between cachectic and non-cachectic patients.

In conclusion, the present study found muscle atrophy and cachexia to be frequent problems in sarcoidosis. Muscle atrophy is associated with worse lung function and exercise capacity compared to normal muscle status, whereas the cachectic patients were the group with the most severe pulmonary disease. Inflammatory status did not discriminate for muscle atrophy. Prospective studies with longitudinal design are needed to investigate the prevalence of cachexia and muscle atrophy and their association with disease activity and severity.

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REFERENCES

- Hunninghake GW, Costabel U, Ando M, et al. ATS/ERS/WASOG statement on sarcoidosis. American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and other Granulomatous Disorders. *Sarcoidosis Vasc Diffuse Lung Dis* 1999; 16 (2): 149-73.
- Iannuzzi MC, Fontana JR. Sarcoidosis: clinical presentation, immunopathogenesis, and therapeutics. *Jama* 2011; 305 (4): 391-9.
- Boots AW, Drent M, Swennen EL, Moonen HJ, Bast A, Haenen GR. Antioxidant status associated with inflammation in sarcoidosis: a potential role for antioxidants. *Respir Med* 2009; 103 (3): 364-72.
- Reich JM. On the nature of sarcoidosis. *Eur J Intern Med* 2012; 23 (2): 105-9.
- Baughman RP, Teirstein AS, Judson MA, et al. Clinical characteristics of patients in a case control study of sarcoidosis. *Am J Respir Crit Care Med* 2001; 164 (10 Pt 1): 1885-9.
- Sharma OP. Fatigue and sarcoidosis. *Eur Respir J* 1999; 13 (4): 713-4.
- Wirnsberger RM, De Vries J, Breteler MH, Van Heck GL, Wouters EF, Drent M. Evaluation of quality of life in sarcoidosis patients. *Respir Med* 1998; 92 (5): 750-6.
- James DG. Complications of sarcoidosis. *Chronic fatigue syndrome. Sarcoidosis* 1993; 10 (1): 1-3.
- Drent M, Lower EE, De Vries J. Sarcoidosis-associated fatigue. *Eur Respir J* 2012; 40 (1): 255-63.
- Wirnsberger RM, De Vries J, Wouters EF, Drent M. Clinical presentation of sarcoidosis in The Netherlands an epidemiological study. *Neth J Med* 1998; 53 (2): 53-60.
- Marcellis RG, Lenssen AF, Elfferich MD, et al. Exercise capacity, muscle strength and fatigue in sarcoidosis. *Eur Respir J* 2011; 38 (3): 628-34.
- Alhamad EH. The six-minute walk test in patients with pulmonary sarcoidosis. *Ann Thorac Med* 2009; 4 (2): 60-4.
- Baughman RP, Sparkman BK, Lower EE. Six-minute walk test and health status assessment in sarcoidosis. *Chest* 2007; 132 (1): 207-13.
- Wirnsberger RM, Drent M, Hekelaar N, et al. Relationship between respiratory muscle function and quality of life in sarcoidosis. *Eur Respir J* 1997; 10 (7): 1450-5.
- Engelen MP, Schols AM, Baken WC, Wesseling GJ, Wouters EF. Nutritional depletion in relation to respiratory and peripheral skeletal muscle function in out-patients with COPD. *Eur Respir J* 1994; 7 (10): 1793-7.
- Schols AM, Soeters PB, Dingemans AM, Mostert R, Frantzen PJ, Wouters EF. Prevalence and characteristics of nutritional depletion in patients with stable COPD eligible for pulmonary rehabilitation. *Am Rev Respir Dis* 1993; 147 (5): 1151-6.
- Remels AH, Gosker HR, Langen RC, Schols AM. The mechanisms of cachexia underlying muscle dysfunction in COPD. *J Appl Physiol* 2013; 114 (9): 1253-62.
- Van Bokhorst-De van der Schueren MA, Konijn NP, Bultink IE, Lems WF, Earthman CP, Van Tuyl LH. Relevance of the new pre-cachexia and cachexia definitions for patients with rheumatoid arthritis. *Clin Nutr* 2012; 31 (6): 1008-10.
- Rajbhandary R, Khezri A, Panush RS. Rheumatoid cachexia: what is it and why is it important? *J Rheumatol* 2011; 38 (3): 406-8.
- Fanzani A, Conraads VM, Penna F, Martinet W. Molecular and cellular mechanisms of skeletal muscle atrophy: an update. *J Cachexia Sarcopenia Muscle* 2012; 3 (3): 163-79.
- Evans WJ, Morley JE, Argiles J, et al. Cachexia: a new definition. *Clin Nutr* 2008; 27 (6): 793-9.
- Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. *Age Ageing* 2010; 39 (4): 412-23.
- Rom O, Kaisari S, Aizenbud D, Reznick AZ. Sarcopenia and smoking: a possible cellular model of cigarette smoke effects on muscle protein breakdown. *Ann N Y Acad Sci* 2012; 1259: 47-53.
- Valeyre D, Soler P, Clerici C, et al. Smoking and pulmonary sarcoidosis: effect of cigarette smoking on prevalence, clinical manifestations, alveolitis, and evolution of the disease. *Thorax* 1988; 43 (7): 516-24.
- Newman LS, Rose CS, Bresnitz EA, et al. A case control etiologic study of sarcoidosis: environmental and occupational risk factors. *Am J Respir Crit Care Med* 2004; 170 (12): 1324-30.
- Marcellis RG, Lenssen AF, De Vries GJ, et al. Is there an added value of cardiopulmonary exercise testing in sarcoidosis patients? *Lung* 2013; 191 (1): 43-52.
- Drent M, Wirnsberger RM, De Vries J, Van Diejen-Visser MP, Wouters EF, Schols AM. Association of fatigue with an acute phase response in sarcoidosis. *Eur Respir J* 1999; 13 (4): 718-22.
- Lukaski HC, Bolonchuk WW, Hall CB, Siders WA. Validation of tetrapolar bioelectrical impedance method to assess human body composition. *J Appl Physiol* 1986; 60 (4): 1327-32.
- Schols AM, Wouters EF, Soeters PB, Westerterp KR. Body composition by bioelectrical-impedance analysis compared with deuterium dilution and skinfold anthropometry in patients with chronic obstructive pulmonary disease. *Am J Clin Nutr* 1991; 53 (2): 421-4.
- Schutz Y, Kyle UU, Pichard C. Fat-free mass index and fat mass index percentiles in Caucasians aged 18-98 y. *Int J Obes Relat Metab Disord* 2002; 26 (7): 953-60.
- De Vries J, Michielsen H, Van Heck GL, Drent M. Measuring fatigue in sarcoidosis: the Fatigue Assessment Scale (FAS). *Br J Health Psychol* 2004; 9 (Pt 3): 279-91.
- Michielsen HJ, De Vries J, Drent M, Peros-Golubicic T. Psychometric qualities of the Fatigue Assessment Scale in Croatian sarcoidosis patients. *Sarcoidosis Vasc Diffuse Lung Dis* 2005; 22 (2): 133-8.
- Rothkrantz-Kos S, Van Diejen-Visser MP, Mulder PG, Drent M. Potential usefulness of inflammatory markers to monitor respiratory functional impairment in sarcoidosis. *Clin Chem* 2003; 49 (9): 1510-7.
- Agostini C, Trentin L, Facco M, et al. Role of IL-15, IL-2, and their receptors in the development of T cell alveolitis in pulmonary sarcoidosis. *J Immunol* 1996; 157 (2): 910-8.
- Hunninghake GW, Bedell GN, Zavala DC, Monick M, Brady M. Role of interleukin-2 release by lung T-cells in active pulmonary sarcoidosis. *Am Rev Respir Dis* 1983; 128 (4): 634-8.
- Muller-Quernheim J. Serum markers for the staging of disease activity of sarcoidosis and other interstitial lung diseases of unknown etiology. *Sarcoidosis Vasc Diffuse Lung Dis* 1998; 15 (1): 22-37.
- Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J Suppl* 1993; 16: 5-40.
- ATS/ACCP Statement on cardiopulmonary exercise testing. American Thoracic Society/American College of Chest Physicians. *Am J Respir Crit Care Med* 2003; 167 (2): 211-77.
- ATS statement: guidelines for the six-minute walk test. American Thoracic Society. *Am J Respir Crit Care Med* 2002; 166 (1): 111-7.
- Enright PL. The six-minute walk test. *Respir Care* 2003; 48 (8): 783-5.
- Enright PL, Sherrill DL. Reference equations for the six-minute walk in healthy adults. *Am J Respir Crit Care Med* 1998; 158 (5 Pt 1): 1384-7.
- Werle S, Goldhahn J, Drerup S, Simmen BR, Sprott H, Herren DB. Age- and gender-specific normative data of grip and pinch strength in a healthy adult Swiss population. *J Hand Surg Eur Vol* 2009; 34 (1): 76-84.
- Mathiowetz V, Kashman N, Volland G, Weber K, Dowe M, Rogers S. Grip and pinch strength: normative data for adults. *Arch Phys Med Rehabil* 1985; 66 (2): 69-74.

44. Black LF, Hyatt RE. Maximal respiratory pressures: normal values and relationship to age and sex. *Am Rev Respir Dis* 1969; 99 (5): 696-702.
45. Vermeeren MA, Creutzberg EC, Schols AM, et al. Prevalence of nutritional depletion in a large out-patient population of patients with COPD. *Respir Med* 2006; 100 (8): 1349-55.
46. Schols AM, Broekhuizen R, Weling-Scheepers CA, Wouters EF. Body composition and mortality in chronic obstructive pulmonary disease. *Am J Clin Nutr* 2005; 82 (1): 53-9.
47. Decramer M, Lacquet LM, Fagard R, Rogiers P. Corticosteroids contribute to muscle weakness in chronic airflow obstruction. *Am J Respir Crit Care Med* 1994; 150 (1): 11-6.
48. Bernard S, LeBlanc P, Whittom F, et al. Peripheral muscle weakness in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998; 158 (2): 629-34.
49. Waatevik M, Johannessen A, Hardie JA, et al. Different COPD disease characteristics are related to different outcomes in the 6-minute walk test. *Copd* 2012; 9 (3): 227-34.
50. Hillman CM, Heinecke EL, Hii JW, Cecins NM, Jenkins SC, Eastwood PR. Relationship between body composition, peripheral muscle strength and functional exercise capacity in patients with severe chronic obstructive pulmonary disease. *Intern Med J* 2012; 42 (5): 578-81.
51. De Kleijn WP, De Vries J, Lower EE, Elfferich MD, Baughman RP, Drent M. Fatigue in sarcoidosis: a systematic review. *Curr Opin Pulm Med* 2009; 15 (5): 499-506.
52. De Vries J, Rothkrantz-Kos S, Van Dieijen-Visser MP, Drent M. The relationship between fatigue and clinical parameters in pulmonary sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2004; 21 (2): 127-36.
53. Spruit MA, Thomeer MJ, Gosselink R, et al. Skeletal muscle weakness in patients with sarcoidosis and its relationship with exercise intolerance and reduced health status. *Thorax* 2005; 60 (1): 32-8.
54. Allaire J, Maltais F, Doyon JF, et al. Peripheral muscle endurance and the oxidative profile of the quadriceps in patients with COPD. *Thorax* 2004; 59 (8): 673-8.
55. Serres I, Gautier V, Varray A, Prefaut C. Impaired skeletal muscle endurance related to physical inactivity and altered lung function in COPD patients. *Chest* 1998; 113 (4): 900-5.
56. Boots AW, Drent M, De Boer VC, Bast A, Haenen GR. Quercetin reduces markers of oxidative stress and inflammation in sarcoidosis. *Clin Nutr* 2011; 30 (4): 506-12.
57. Kao CC, Hsu JW, Bandi V, Hanania NA, Kheradmand F, Jahoor F. Resting energy expenditure and protein turnover are increased in patients with severe chronic obstructive pulmonary disease. *Metabolism* 2011; 60 (10): 1449-55.
58. Grutters JC, Van den Bosch JM. Corticosteroid treatment in sarcoidosis. *Eur Respir J* 2006; 28 (3): 627-36.
59. Paddon-Jones D, Sheffield-Moore M, Cree MG, et al. Atrophy and impaired muscle protein synthesis during prolonged inactivity and stress. *J Clin Endocrinol Metab* 2006; 91 (12): 4836-41.
60. Korenromp IH, Grutters JC, Van den Bosch JM, Heijnen CJ. Post-inflammatory fatigue in sarcoidosis: personality profiles, psychological symptoms and stress hormones. *J Psychosom Res* 2012; 72 (2): 97-102.
61. Mastorakos G, Paltoglou G, Greene M, et al. Inappropriately normal plasma ACTH and cortisol concentrations in the face of increased circulating interleukin-6 concentration in exercise in patients with sarcoidosis. *Stress* 2013; 16 (2): 202-10.
62. Langen RC, Haegens A, Vernooij JH, et al. NF-kappaB activation is required for the transition of pulmonary inflammation to muscle atrophy. *Am J Respir Cell Mol Biol* 2012; 47 (3): 288-97.
63. Zoico E, Roubenoff R. The role of cytokines in regulating protein metabolism and muscle function. *Nutr Rev* 2002; 60 (2): 39-51.
64. Langen RC, Schols AM, Kelders MC, Van der Velden JL, Wouters EF, Janssen-Heininger YM. Muscle wasting and impaired muscle regeneration in a murine model of chronic pulmonary inflammation. *Am J Respir Cell Mol Biol* 2006; 35 (6): 689-96.
65. Wouters EF, Groenewegen KH, Dentener MA, Vernooij JH. Systemic inflammation in chronic obstructive pulmonary disease: the role of exacerbations. *Proc Am Thorac Soc* 2007; 4 (8): 626-34.
66. Drent M, Van den Berg R, Haenen GR, Van den Berg H, Wouters EF, Bast A. NF-kappaB activation in sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2001; 18 (1): 50-6.
67. Rahman I. Oxidative stress, transcription factors and chromatin remodeling in lung inflammation. *Biochem Pharmacol* 2002; 64 (5-6): 935-42.
68. Van den Borst B, Gosker HR, Schols AM. Central fat and peripheral muscle: partners in crime in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2013; 187 (1): 8-13.
69. Zafon C. Fat and aging: a tale of two tissues. *Curr Aging Sci* 2009; 2 (2): 83-94.
70. Fuller NJ, Jebb SA, Laskey MA, Coward WA, Elia M. Four-component model for the assessment of body composition in humans: comparison with alternative methods, and evaluation of the density and hydration of fat-free mass. *Clin Sci (Lond)* 1992; 82 (6): 687-93.
71. Van Loan MD. Is dual-energy X-ray absorptiometry ready for prime time in the clinical evaluation of body composition? *Am J Clin Nutr* 1998; 68 (6): 1155-6.
72. Wilson JP, Mulligan K, Fan B, et al. Dual-energy X-ray absorptiometry-based body volume measurement for 4-compartment body composition. *Am J Clin Nutr* 2012; 95 (1): 25-31.
73. Pahor M, Manini T, Cesari M. Sarcopenia: clinical evaluation, biological markers and other evaluation tools. *J Nutr Health Aging* 2009; 13 (8): 724-8.