

Concise Report

Preliminary evidence for cachexia in patients with well-established ankylosing spondylitis

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Objectives. Cachexia, defined as an accelerated loss of skeletal muscle in the context of a chronic inflammatory response, is common in rheumatoid arthritis but it has not been demonstrated in patients with ankylosing spondylitis (AS). The aim of this study was to determine muscle wasting and its functional consequences in a group of patients with well-established AS.

Methods. Nineteen male patients (mean age 53 yrs) with long-standing AS (mean disease duration 19 yrs) and radiological changes (84% had one or more syndesmophytes) were compared with 19 age-matched healthy males with similar levels of habitual physical activity. Body composition was assessed by dual energy X-ray absorptiometry. Muscle strength was measured by isokinetic knee extension and hand grip dynamometry, and by 30 s arm curl and chair sit-to-stand tests.

Results. AS patients showed a statistically and clinically significant 12% reduction in arms and legs lean mass, a proxy measure of total body skeletal muscle mass, compared with healthy controls ($P < 0.05$). This muscle loss was significantly associated with reduced upper and lower body strength (correlation coefficients ranging between 0.37 and 0.79, $P < 0.05$).

Conclusion. These results provide preliminary evidence that cachexia is a functionally relevant systemic complication of AS, particularly in patients with long-standing disease and radiological changes. Progressive resistance training and other interventions aimed at stimulating skeletal muscle growth might be beneficial in this population, and further studies on the pathophysiology of cachexia in AS patients are needed.

KEY WORDS: Ankylosing spondylitis, Body composition, Cachexia, Physical function, Skeletal muscle, Disability, Strength, Lean mass, Body fat, Spine.

Introduction

Cachexia has been defined as ‘an accelerated loss of skeletal muscle in the context of a chronic inflammatory response’ [1]. The direct consequence of this catabolic process is muscle atrophy and thus weakness, physical disability, increased rate of infections and premature death [1, 2].

Cachexia is a common feature of other systemic diseases such as rheumatoid arthritis (RA), and is attributed to elevated circulating concentrations of tumor necrosis factor (TNF) and other pro-inflammatory cytokines [1, 2]. These cytokines are also elevated in the serum of patients with ankylosing spondylitis (AS) [3] and, consequently, muscle wasting would be expected in this population. However, body composition studies have not consistently demonstrated a reduction in muscle mass in AS patients [4–8].

Possible explanations for these conflicting results are the variety of methods used to assess body composition, and differences in the disease duration and severity of patients studied. In addition, previous investigators have not reported the effects of AS on regional body composition. This is important since arms and legs (appendicular) lean mass is a better proxy measure of total body skeletal muscle mass [9] than total lean mass or fat-free mass. Furthermore, dual energy X-ray absorptiometry (DXA) measures of body composition including the trunk might be slightly affected by the kyphosis of the spine [10]. Trunk lean mass could also

be reduced by spine immobility rather than the metabolic consequences of systemic inflammation.

Therefore, the aim of this study was to determine loss of appendicular lean mass and its functional consequences in a group of patients with long-standing AS and radiological changes.

Methods

Subjects

A convenient sample of 19 ambulant male patients with AS according to the Rome Criteria [11] was recruited from the Rheumatology Department of Ysbytu Gwynedd in North Wales (UK). A group of 19 age-matched (within 5 yrs) healthy males was recruited from the same local community to serve as controls. Exclusion criteria were the presence of any other catabolic disease, any condition preventing safe participation in the study, and participation in regular and intense physical training. The study was approved by the Ethics Committee of the North West Wales NHS Trust and all volunteers signed a written consent obtained according to the Declaration of Helsinki.

For the present investigation a sample size of 32 was estimated on the basis of a published study comparing appendicular lean mass by DXA (our main outcome variable) between healthy men

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($n=246$) and men with catabolic conditions ($n=213$) with a similar age range [12]. From this study, a Cohen's d of 1.028 was calculated and used to estimate an adequate sample size for type I and II errors of 5 and 20%, respectively (two-tailed). To account for potential dropouts, 38 subjects were recruited.

Measurements

Demographics and information on disease duration and current therapies were obtained from patients or their medical records. Disease activity was assessed by the Bath AS disease activity index (BASDAI). The functional consequences of the disease were measured by the Bath AS functional index (BASFI). Sacroiliitis and hip involvement were assessed on anteroposterior pelvic radiographs and graded according to the New York Scale. Lumbar involvement was measured by the Bath AS Radiology Index (BASRI). Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were assessed using standard laboratory techniques. Physical activity levels at work and during leisure-time were quantified using a standardized questionnaire [13]. The sum of these two scores was then used as a measure of the total level of physical activity on a 7-point scale ranging from 2 (sedentary) to 8 (highly active). Standing height, knee height and body mass were obtained using standard anthropometric procedures. To eliminate the effect of the spondylitic kyphosis, the Han equation [14] was used to predict standing height from knee height when calculating body mass index (BMI).

Total and regional (arms, legs, trunk and head) fat mass, lean mass and bone mineral content were measured by whole-body DXA (QDR 1500, software version V5.72, Hologic Inc., Bedford MA). Validity data obtained in our lab demonstrated a Pearson correlation coefficient between fat-free mass by DXA and by another criterion method, underwater weighing, of 0.98 ($P < 0.001$) and a bias ($\pm 95\%$ limits of agreement) of -1.2 kg (± 3.5 kg) in seven young and healthy volunteers. Reliability data obtained in our lab on a group of 10 patients with RA tested on two occasions, separated by 3 months, gave a coefficient of variation for appendicular lean mass by DXA of 1.8%.

Maximal voluntary strength of the knee extensors (dominant leg) was measured at 60° per second using an isokinetic dynamometer (Kin-com, Chattanooga, Tennessee USA). Maximal voluntary grip strength of the dominant hand was measured with a Grip-A dynamometer (Takey, Kiki Kogyo, Japan). Upper and lower body functional strength were assessed using the 30s arm curl and chair sit-to-stand tests developed by Rikli and Jones [15].

Statistical analysis

Descriptive data are presented as mean \pm s.d. for normally distributed variables or median and (interquartile range) for not normally distributed variables. Comparisons between groups were performed using two-tailed paired Student's t -tests or Wilcoxon signed-rank tests as appropriate. Pearson correlation coefficient was used to examine the relationships between appendicular lean mass and measures of muscle strength. Statistical significance was set at 0.05 for all analyses.

Results

Patients included in this study had long-standing (disease duration 19 ± 13 yrs) and moderately active AS (BASDAI 4.6 ± 2.1 , ESR 18.6 ± 15.5 mm/h, CRP 11.7 ± 22.4 mg/l) with significant radiological changes [New York Sacroiliitis Score 3.5 (1.0), BASRI Lumbar Spine 4.0 (2.0)] and some functional impairment (BASFI 3.9 ± 2.0). Most patients were receiving or had received NSAIDs and several had received or were receiving sulphasalazine. None of the subjects had used corticosteroids or other drugs known to influence muscle mass (e.g. anabolic steroids).

TABLE 1. Subject characteristics and body composition analysis*

Variable	AS patients ($n=19$)	Controls ($n=19$)	P
Age (yrs)	53 ± 12	54 ± 10	0.339
Standing height (cm)	168 ± 6	174 ± 7	<0.001
Knee height (cm)	51.9 ± 2.4	52.7 ± 2.7	0.179
Body mass (kg)	75.8 ± 12.1	82.3 ± 11.1	0.086
Body mass index (kg/m^2) [#]	26.0 ± 4.2	27.1 ± 3.0	0.357
Physical activity (2–8)	4.2 (1)	4.6 (1)	0.052
Total lean body mass (kg)	51.8 ± 6.3	58.2 ± 7.4	0.002
Appendicular lean mass (kg)	21.9 ± 2.8	24.9 ± 4.2	0.005
Total fat mass (kg)	20.4 ± 7.4	20.1 ± 7.7	0.896
Trunk fat (kg)	10.8 ± 5.0	10.7 ± 4.8	0.917
Total BMC (kg)	2.76 ± 0.36	2.94 ± 0.45	0.200

*Values are mean \pm s.d. or median and (interquartile range).

[#]Calculated using predicted standing height (see 'Methods' section for further details).

BMC, bone mineral content.

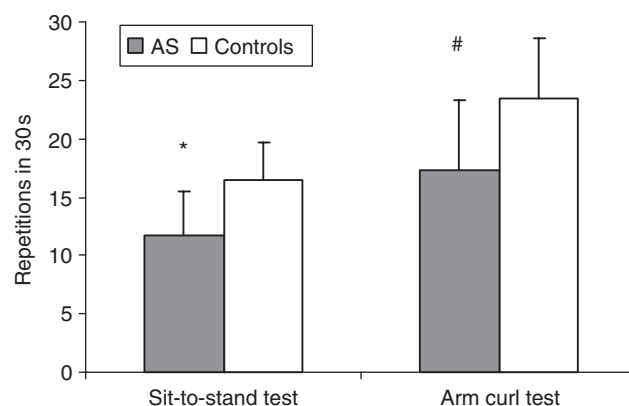


FIG. 1. Differences in upper and lower body functional strength between AS patients and controls. Values are mean \pm s.d. * $P < 0.001$; # $P = 0.002$.

Subjects' demographic and anthropometric characteristics and habitual physical activity levels are shown in Table 1. Except for standing height, the two groups were well-matched. However, since knee height was similar, the difference in standing height is the evidence of kyphosis rather than different stature. Therefore, body composition data were not normalized by height.

The results of the body composition analysis are also shown in Table 1. As expected, there were significant differences between patients and controls in both total and appendicular lean mass, but not in total and trunk fat mass, and total bone mineral content.

With the exception of handgrip strength (AS = 40.1 ± 8.0 kg, controls = 40.4 ± 8.9 kg, $P = 0.905$), patients were weaker than controls. In fact both knee extensors strength (AS = 181 ± 67 Nm, controls = 228 ± 72 Nm, $P = 0.040$) and all functional strength tests scores (Fig. 1) were significantly lower in AS patients compared with healthy controls.

Appendicular lean mass was significantly correlated with knee extensors strength ($R = 0.79$, $P < 0.001$), handgrip strength ($R = 0.37$, $P = 0.024$), arm curl test ($R = 0.49$, $P = 0.002$) and chair sit-to-stand test ($R = 0.42$, $P = 0.008$).

Discussion

This is the first study to demonstrate a statistically significant reduction in total (6 kg) and appendicular lean mass in patients

with AS. These results are in contrast with those of previous DXA studies on the effects of AS on body composition, which found a statistically non-significant reduction of ~3 kg of total lean mass [5, 8]. The most likely explanation for this disparity in findings is the difference in disease severity and duration. Dos Santos *et al.* [8] excluded patients with syndesmophytes and in the study of Toussiro *et al.* [5] only 27% of the patients had at least one syndesmophyte. In contrast, 84% of our patients had one or more syndesmophytes. Furthermore, patients in the studies of Toussiro *et al.* [5] and Dos Santos *et al.* [8] had mean disease durations of 11 and 8 yrs, respectively, each considerably less than our patients (19 yrs).

As in RA and other systemic diseases, the chronic inflammatory response is likely to be the major cause of muscle wasting in AS patients [1, 2]. This hypothesis is supported by the results of a recent study demonstrating significant increases in total lean mass in a group of patients with spondyloarthritis after 12 months' treatment with either etanercept or infliximab [16].

However, alternative explanations for the observed reduction in appendicular lean mass should be excluded before cachexia can be established in this population. We controlled for sarcopenia (the age-related loss of skeletal muscle mass and function) by matching patients and controls for age. We also controlled for the confounding effects of habitual physical activity on body composition by selecting a homogeneous group of ambulant but not extremely active subjects, and by assessing physical activity levels using a simple but physiologically validated questionnaire [13]. Although the difference in total physical activity score approached statistical significance ($P=0.052$), its magnitude (0.4) is not sufficient to categorize our AS patients at a lower level of physical activity either at work or during their leisure-time compared with our healthy controls. Therefore, we considered this statistically non-significant difference to be of little physiological importance and for this reason we did not include it as a covariate in our analyses. More importantly, the levels of both work (e.g. *sitting or standing, some walking*) and leisure-time physical activity (e.g. *some physical activity for at least 4 h per week*) necessary to produce the median score of 4.2, reported by our AS patients are well above the minimal levels of physical activity necessary to induce disuse atrophy (e.g. prolonged bed rest) [17]. Although we cannot exclude that our AS patients with long-standing disease have had intermittent periods of significant inactivity, it is well-known that disuse atrophy quickly recovers after re-ambulation [17]. Consequently, we believe disuse due to pain and disability is unlikely to have played a major role in the large difference in appendicular lean mass observed between patients and controls. Although we did not measure dietary intake, malnutrition also seems an unlikely cause of muscle wasting in our AS patients given the selective loss of lean mass, a mean BMI of 26 kg/m² and an average of 27% body fat. Consequently, we believe AS should be tentatively included in the list of conditions complicated by cachexia as defined by Kotler [1]. Nevertheless, further studies are required to provide conclusive evidence of cachexia in this population by investigating other cardinal features of this complex syndrome such as elevated basal metabolic rate and accelerated muscle protein breakdown.

Regardless of its cause, the average 12% reduction in appendicular lean mass we measured in our AS patients would be expected to have serious clinical consequences. In fact, muscle losses of 5 and 40% have been associated with reduced physical function and premature death, respectively [1, 2]. We also found significant correlations between appendicular lean mass and various measures of upper and lower body strength in our subjects. Consequently, wasting of limb muscles may be an important and novel therapeutic target to reduce physical disability in AS patients, and future studies should investigate various anabolic interventions such as progressive resistance training and dietary supplementation whose efficacy and safety have been demonstrated in other rheumatic diseases [18, 19].

Further research to confirm our preliminary evidence of cachexia is also warranted given the important therapeutic implications of establishing the catabolic effects of TNF and other cytokines in AS patients.

<i>Rheumatology</i>	Key message
	<ul style="list-style-type: none"> • Patients with long-standing AS and radiological changes have significant losses of arms and legs lean mass. This muscle wasting is significantly associated with reduced muscle strength.

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