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Physical Activity and Body Composition in Patients With Ankylosing Spondylitis

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Objective. **Patients with ankylosing spondylitis (AS) are at risk for accelerated muscle loss and reduced physical activity. Accurate data are needed on body composition and physical activity in this patient group. The purpose of this study was to investigate body composition and objectively assessed physical activity in patients with AS.**

Methods. **Twenty-five AS patients (15 men, mean ± SD age 48 ± 11 years) were compared with 25 healthy adults matched for age, sex, and body mass index. Body composition was measured using a 3-compartment model based on air-displacement plethysmography to assess body volume and deuterium dilution to assess total body water. The fat-free mass index (FFMI; fat-free mass divided by height squared) and the percent fat mass (%FM) were calculated. Daily physical activity was assessed for 7 days using a triaxial accelerometer and physical fitness with an incremental test until exertion on a bicycle ergometer. Blood samples were taken to determine C-reactive protein (CRP) level and tumor necrosis factor α.**

Results. **Accelerometer output (kilocounts/day) showed the same physical activity level for patients and controls (mean ± SD 319 ± 105 versus 326 ± 66). There was no difference in the FFMI or %FM between the patients and controls. Physical activity was positively related to the FFMI (partial $R = 0.38$, $P = 0.01$) and inversely related to CRP level ($R = -0.39$, $P < 0.01$), independent of group. CRP level was inversely related to the FFMI, but the effect was less strong than with physical activity (partial $R = -0.31$, $P = 0.03$).**

Conclusion. **Daily physical activity may help preserve fat-free mass in patients with AS.**

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disorder of the axial skeleton and in up to 20% of patients, also of the peripheral joints. Patients undergo pain, stiffness, and reduced mobility of the spine and joints. (1). As a consequence, patients with AS experience limitations in physical activities and reduced quality of life (2). Given the chronic inflammation and risk of reduced physical activity, patients are also at risk for accelerated muscle loss. In chronic diseases, the loss of muscle mass, often referred to as cachexia, is a relevant systemic complication leading to reduced muscle strength and endurance, decreased physical activity and fitness, and hence reduced functional independency and quality of life. In patients with rheumatoid arthritis (RA), muscle loss contributes to a 2 to 5 times higher all-cause mortality and reduced life expectancy of 3 to 18 years (3). In AS, evidence for muscle loss is less compelling. Marcora et al showed that patients with well-established AS had a significant reduction of 12% in lean mass of the arms and legs (4). In contrast, 2 studies by Toussirot et al showed no difference in fat-free mass (FFM) or fat mass (FM) between patients with AS and controls (5,6). Therefore, it remains unclear whether patients with AS are also at risk for "rheumatoid" cachexia.

The proinflammatory cytokine tumor necrosis factor α (TNFα), which plays a central role in the pathogenesis of inflammatory rheumatic diseases such as RA and AS, has been shown to be one of the key players in the pathogenesis of accelerated muscle loss (1,7). Although the exact underlying pathophysiologic mechanism remains unclear, it is known that TNFα can induce muscle loss both by stimulating muscle protein breakdown and inhibiting myogenic differentiation (8). Walsmith et al showed an inverse relationship between body cell mass and TNFα (7) in patients with RA. To our knowledge, this relationship has never been studied in AS.

Physical activity, on the other hand, is the major stimulus for muscle anabolism and therefore may be of high importance in the prevention of muscle loss. Physical

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Significance & Innovations

- Objectively measured physical activity showed that patients with ankylosing spondylitis (AS) are equally active as healthy controls matched for age, sex, and body mass index.
- There was no evidence for accelerated muscle loss in patients with AS; the fat-free mass index was the same in patients and controls.
- Physical activity was positively associated with the fat-free mass index in both patients and healthy controls.
- Physical activity was inversely related to C-reactive protein level in both patients and healthy controls.

activity includes sports and exercise but also nonsports activities such as occupational, leisure time, and household activities (9). Chronic diseases such as AS interfere with patients' physical functioning and quality of life. As a consequence, patients are at risk for physical inactivity, which may contribute to the risk for long-term complications such as cardiovascular disease (10) and osteoporosis (11). However, to our knowledge, no objectively assessed physical activity data are available for patients with AS. Although self-reported measures of physical activity can provide some information on the amount and type of physical activity performed, it remains subjective. Objective monitoring of physical activity is limited to assessing energy expenditure using doubly labeled water, heart rate monitoring, or accelerometry (activity monitors). Doubly labeled water is the gold standard to assess total energy expenditure over a period of 2–3 weeks in daily life (12). Accelerometers, on the other hand, measure actual body movement and are, when properly validated, objective and precise tools to assess free-living physical activity with information on activity patterns in terms of frequency, duration, and intensity (12).

Therefore, the aim of the current study was 3-fold: 1) to compare body composition between patients with AS and healthy controls, 2) to compare daily physical activity and physical fitness between patients and controls, and 3) to investigate the relationship between body composition, serum TNFα levels, and physical activity as possible determinants of muscle loss in patients with AS.

SUBJECTS AND METHODS

Subjects. Twenty-five patients (15 men) with AS according to the modified New York criteria (13), with a mean ± SD age of 48 ± 11 years and a disease duration of at least 5 years after diagnosis, were recruited through the rheumatology departments of Maastricht University Medical Centre, Máxima Medisch Centrum, Eindhoven, and Atrium Medisch Centrum, Heerlen, The Netherlands. Patients were excluded when they were receiving anti-TNFα therapy or had comorbidities that might affect energy balance, such as inflammatory bowel disease or malignancies. Patients were recruited by letters of invitation and flyers and poster advertisements placed at the rheumatology unit of the hospital. Patients were compared with 25 healthy volunteers matched for age, sex, and body mass index (BMI). For 14 of 25 patients, the matched control was a healthy first-degree relative. Other control subjects were recruited from the general population using poster advertisements around the university. All of the analyses presented in this study were unaffected by the fact that part of the group was related; therefore, all data are presented for the entire group. For 2 subjects (1 patient, 1 control), no physical activity data were available, so all analyses that include physical activity are based on 48 subjects.

The study was approved by the Medical Ethics Committee of Maastricht University Medical Centre and registered in the public trial registry Centrale Commissie Mensgebonden Onderzoek (online at www.ccmo-online.nl).

Body composition. Height was measured to the nearest 0.1 cm (Seca-stadiometer, model 220).

Total body water was measured using deuterium dilution according to the Maastricht protocol (14). A background urine sample was collected in the evening before the consumption of approximately 75 ml of deuterium-enriched (4.25%) water resulting in an enrichment of 50–100 parts per million. In the morning, after an overnight fast, the second voiding was collected.

The same morning, body volume was assessed using air-displacement plethysmography (Bod Pod, Life measurement), according to the manufacturer's instructions and described by Dempster and Aitkens (15). All of the subjects wore tightly fitting bathing suits and a swim cap. Subjects had not engaged in exercise at least 1 hour prior to the test. Body mass was measured to the nearest 0.1 kg with subjects in the bathing suit using the calibrated scale included in the Bod Pod technology. Body density was calculated as body mass divided by body volume.

The percent FM (%FM) was calculated from body density and total body water using Siri's 3-compartment (3-C) model (16). From the %FM, absolute FM and FFM were derived, and the FFM index (FFMI) and FM index (FMI) were calculated as FFM/height^2 and FM/height^2, respectively. Figure 1 provides an overview of all of the body composition parameters and how they were calculated.

Physical activity. Physical activity was measured using the triaxial accelerometer for movement registration (Tracmor; Philips Research). The Tracmor contains 3 uniaxial piezoelectric accelerometers, measures 7.2 × 2.6 × 0.7 cm, and weighs 22 gm (battery included). It is attached to the lower back of the subject by means of an elastic belt, measuring all accelerations in the anteroposterior, mediolateral, and longitudinal axis of the trunk. Subjects were instructed to wear the Tracmor for 7 consecutive days, during waking hours, except during water activities. The Tracmor provided minute-by-minute data, which were downloaded to computer files after 7 days. The Tracmor has previously been validated against doubly labeled wa-

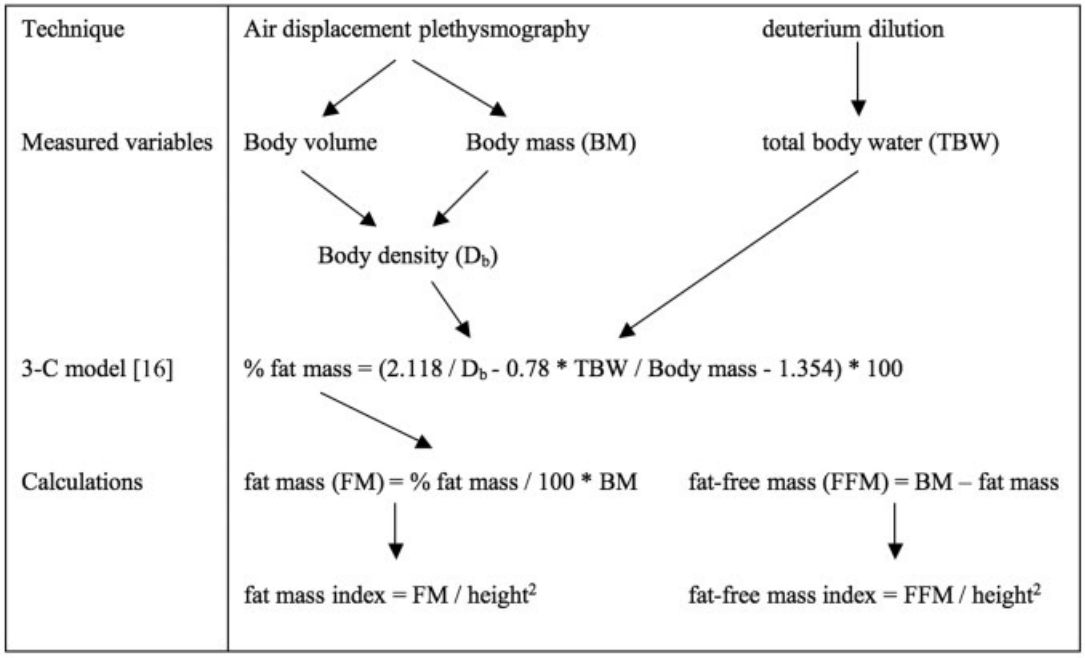

Figure 1. Flow chart showing how body composition parameters were measured and calculated. 3-C = 3-compartment.

ter, the gold standard to assess daily life energy expenditure (12,17). From this validation study, a formula was developed to translate accelerometer output (activity counts) to the physical activity level (PAL = total daily energy expenditure divided by basal metabolic rate). The PAL was calculated as:

$$PAL = 1.267 + 1.437 \times 10^{-3} \times \text{activity counts (kilocounts/day)} \quad \text{(formula 1)}$$

Tracmor output, expressed as kilocounts per day, was used for all statistical analyses. The PAL as calculated above was only used to allow comparison of the PAL with other studies.

Physical fitness. Maximal oxygen uptake ($V_{O_{2max}}$) was assessed using an incremental bicycle ergometer test until maximal exertion according to the protocol by Kuipers et al (18). After a 5-minute warm-up at 75 W for women and 100 W for men, resistance was increased by 50 W every 2.5 minutes. When heart rate reached 160 beats/minutes and/or the respiratory quotient was higher than 1, resistance was increased by 25 W. During the entire test, O_2 consumption and CO_2 production were measured continuously (Omnical 5, Maastricht University) to obtain $V_{O_{2max}}$. Maximal work load (W_{max}) was also calculated as the maximal amount of watts achieved at exertion (18).

Inflammation. Blood samples were taken in the morning after an overnight fast, centrifuged, and stored at −80°C until analysis. C-reactive protein (CRP) level was determined in plasma with a latex-enhanced immunoturbidimetric assay (HORIBA ABX). TNFα was measured in serum using high-sensitivity enzyme-linked immunosorbent assay (ELISA; R&D Systems).

In addition to CRP level, the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), a self-report questionnaire on disease activity, was used. The total BASDAI scores range from 0–10, with higher numbers indicating higher disease activity (19).

Statistics and calculations. All of the variables were checked for normality by visual interpretation of histograms and statistically using the Shapiro-Wilk test. Normally distributed data are shown as the mean ± SD. Not normally distributed variables were transformed using a log transformation (CRP) or a 1/x transformation (TNFα) for analyses and presented as the median (25th, 75th percentiles). Physical activity was compared between the groups using an unpaired *t*-test. $V_{O_{2max}}$ and W_{max} were corrected for FFM and compared between the groups using analysis of covariance (ANCOVA). Linear regression analysis and/or ANCOVA were used to determine significant predictors of the FFMI and to compare body composition between the groups. Specifically, the multivariate relationship between FFMI and physical activity, CRP level, and/or TNFα was explored. The regression models were controlled for the known confounders of the FFMI comprising sex (women have a relatively lower FFM than men) and the FMI (as FM increases, FFM also increases). In a final step, interactions between the independent variables were checked.

RESULTS

Subject characteristics. Subject characteristics are shown in Table 1. There were no differences in age, body mass, or BMI between the groups, but height was significantly lower in patients.

No significant differences were observed between the

Table 1. Subject characteristics*

	Patients (AS)	Controls
Total no. (men/women)	25 (15/10)	25 (15/10)
Age, years	48 ± 11 (23–62)	48 ± 12 (18–65)
Body mass, kg	76.9 ± 15.1 (49.1–109.9)	79.1 ± 11.6 (57.9–102.7)
Height, meters	1.71 ± 0.07 (1.60–1.85)†	1.77 ± 0.08 (1.64–1.89)
BMI, kg/m^2	26.2 ± 5.0 (18.1–39.6)	25.4 ± 3.3 (20.5–31.5)
BASDAI score	4.3 ± 2.2 (1.1–7.3)	–
BASFI score (n = 24 patients)	4.0 ± 2.2 (0.4–7.6)	0.4 ± 1.0 (0.0–5.1)
Time since diagnosis, years	19 ± 12 (5–44)	–
CRP level, median (25th, 75th percentile) (range) mg/liter	3.1 (0.6–8.6) (0.1–25.1)‡	1.8 (0.3–2.7) (0.0–6.0)
TNFα, median (25th, 75th percentile) (range) pg/ml	1.4 (1.0–2.7) (0.5–121.6)	1.3 (0.8–1.7) (0.5–5.8)

* Values are the mean ± SD (range) unless otherwise indicated. AS = ankylosing spondylitis; BMI = body mass index; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; CRP = C-reactive protein; TNFα = tumor necrosis factor α.
† Difference between groups $P = 0.01$.
‡ Difference between groups $P = 0.09$ (analysis of variance with log[CRP]).

patients and controls for CRP level or TNFα, although there was a trend for higher CRP values in patients ($P = 0.09$). Both variables were positively skewed with a number of patients showing high values, as indicated by the range. The mean ± SD BASDAI score for patients was 4.3 ± 2.2 (range 1.1–7.3). The proportion of patients with "active disease" according to the BASDAI (score of >4) was 14 (56%) of 25. The BASDAI and CRP values indicated active disease in a substantial part of the patient population.

Four patients did not report their medication use. Sixteen (76%) of 21 patients used nonsteroidal antiinflammatory drugs (NSAIDs), and 3 of those reported taking NSAIDs only during flare ups. Three (14%) of 21 used disease-modifying antirheumatic drugs.

Body composition. Table 2 shows all of the body composition data for the patients and controls, separated by sex. As expected, women have a lower absolute percent FFM (%FFM) and FFMI and higher %FM and FMI than men. No differences were observed between the patients and controls in FFM, either expressed as the %FFM or the FFMI, or in FM, %FM, or FMI.

Physical activity and fitness. There was no significant difference in accelerometer output between the patients and controls (Table 3). The corresponding mean ± SD PAL calculated from accelerometer output using formula 1 was 1.73 ± 0.15 and 1.74 ± 0.09 for the patients and controls, respectively. Linear regression analysis showed a significant inverse relationship between plasma CRP (log CRP) and physical activity ($R = -0.39$, $P < 0.01$) (Figure 2).

Physical fitness, expressed as $V_{O_{2max}}$ corrected for FFM, tended to be lower in patients than in controls (mean ± SD 2,476 ± 608 versus 2,610 ± 609 ml/minute; $F[1,46] = 2.9$, $P = 0.09$), although the difference was not significant. W_{max} corrected for FFM, as a measure of maximal power output, was also not different between the groups (Table 3).

Determinants of the FFMI. The results from multiple linear regression analysis with the FFMI as the dependent variable are provided in Table 4. After correction for sex and the FMI, physical activity was positively related to the FFMI (partial $R = 0.38$, $P = 0.01$). Group (patient versus control) was not related to the FFMI. Log CRP was negatively correlated with the FFMI (partial $R = -0.31$, $P = 0.03$), again after correcting for sex and FMI, but the effect was not as strong as with physical activity. The relationship between physical activity or CRP and the FFMI was unaffected by group (no interaction). There was no correlation between serum TNFα and the FFMI or the BASDAI and the FFMI.

Table 2. Body composition data for patients and controls and men and women separately*

	Patients		Controls	
	Men	Women	Men	Women
FFM, kg	60.0 ± 7.0†	43.6 ± 4.0	61.8 ± 3.6†	45.8 ± 3.0
FM, kg	21.5 ± 8.4	26.3 ± 12.7	22.7 ± 7.1	25.2 ± 7.5
%FFM	74.3 ± 7.0†	63.9 ± 8.1	73.6 ± 5.5†	65.2 ± 5.9
%FM	25.7 ± 7.0†	36.1 ± 8.1	26.4 ± 5.5†	34.8 ± 5.9
FFMI, kg/m^2	19.7 ± 1.8†	15.7 ± 1.3	18.9 ± 1.3†	16.0 ± 1.1
FMI, kg/m^2	7.1 ± 2.9‡	9.5 ± 4.7	6.9 ± 2.2‡	8.8 ± 2.6

* Values are the mean ± SD. FFM = fat-free mass; FM = fat mass; FFMI = fat-free mass index; FMI = fat mass index.
† Significant sex difference ($P < 0.001$).
‡ Significant sex difference ($P < 0.05$).

Table 3. Physical activity and fitness*

	Patients (AS)	Controls
Physical activity, kilocounts/day	319 ± 105	326 ± 66
PAL	1.73 ± 0.15	1.74 ± 0.09
Vo_{2max}, ml/minute†	2,476 ± 608	2,610 ± 609
W_{max}, watts†	194 ± 61	209 ± 61

* Values are the mean ± SD. AS = ankylosing spondylitis; PAL = physical activity level; Vo_{2max} = maximal oxygen uptake; W_{max} = maximal work load.
† Corrected for fat-free mass using analysis of covariance.

DISCUSSION

This study showed that patients with AS were equally physically active and had the same body composition as age-, sex-, and BMI-matched healthy controls. Independent of group, physical activity was positively related to the FFMI and inversely related to plasma CRP levels. CRP was also inversely related to the FFMI, but the effect was not as strong as with physical activity.

Accelerated muscle loss is observed at a higher age (sarcopenia), and in chronic diseases such as cancer and chronic obstructive pulmonary disease, and is collectively referred to as cachexia (20). In patients with RA, several studies, although not all, have shown evidence for a decreased FFM compared to healthy controls (21–25). In patients with AS, evidence is limited. Two studies by Toussirot et al showed no differences in FFM or FM, as measured with dual x-ray absorptiometry (DXA), between patients and controls (5,6). Sari et al used bioelectrical impedance analysis and found no differences in FFM between patients and controls, but a lower %FM in male patients compared to healthy controls (26). Marcora et al were the first to show a decreased appendicular and total lean mass in male patients with AS, which was related to lower functional strength (4). In the current study, no difference was found in FFM, and also not when corrected for height (FFMI) or expressed as a percentage of total body mass. From the data in Table 3, it is clear that there was also no trend of FFM to be lower in patients, and the FFMI was even slightly higher in patients. Importantly, the observed values of the FFMI correspond to those of a large sample of healthy subjects, with an average FFMI of 19.2 and 15.9 for men and women (ages 35–54 years), respectively (27). The study by Marcora et al (4) included only men that were on average 5 years older than the patients in our study, and patients were not allowed to participate in regular intensity physical activity. The latter is an important difference from the current study. Our inclusion criteria did not pose any limits on participation in physical activity, since one of the aims was to objectively quantify daily PALs in patients with AS.

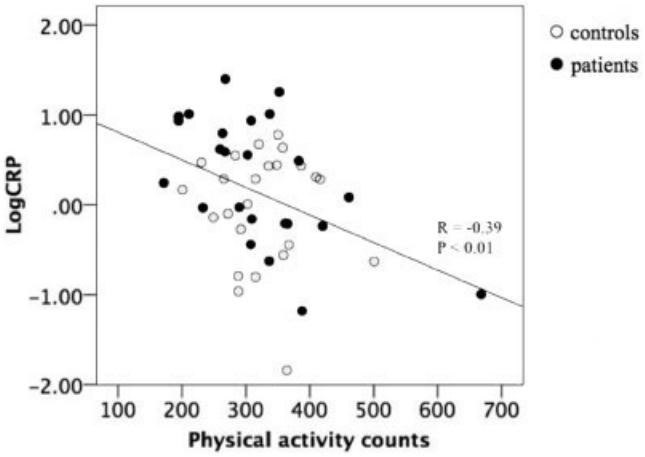

Figure 2. Correlation between C-reactive protein (LogCRP) level and physical activity counts (kilocounts/day). The regression line is based on both groups.

To our knowledge, this is the first study using an objective measure of daily physical activity in this patient group. Patients were shown to be equally active as healthy controls. Furthermore, when the output of the accelerometer was translated to a PAL, the most widely used measure to express physical activity, patients had an average PAL of 1.73. This level of daily physical activity corresponds to a "normal" moderate PAL as observed in the average population (28,29). Interestingly, subjects with a higher PAL also had a higher FFMI, indicating that high daily physical activity, which does not necessarily include sports, helps to preserve FFM.

The lack of difference in physical activity between patients and controls was also supported by the finding that Vo_{2max} was the same in both groups. Toussirot et al assessed physical fitness (Vo_{2max}) in AS patients with a questionnaire and also found no differences between patients and controls (6).

The importance of TNFα in the pathophysiology of AS (1) but also in muscle loss is well known (8,30,31). TNFα

Table 4. Results from multiple regression analysis with the fat-free mass index as the dependent variable

Independent	Coefficient	SE	*P*	Partial R
Constant*	10.91	0.93	< 0.001	
Sex†	4.32	0.33	< 0.001	0.89
FMI, kg/m^2	0.35	0.05	< 0.001	0.72
Physical activity, kilocounts/day	0.005	0.002	0.01	0.38
Model			< 0.001	R = 0.89 (R^2 = 0.80)

* The regression constant is the Y-intercept of the regression line determined by sex, fat mass index (FMI), and physical activity.
† 0 = women, 1 = men.

can induce muscle loss directly by both stimulating muscle protein breakdown and reducing the sensitivity of skeletal muscle cells to anabolic stimuli (32). One possible pathway is that TNFα activates NF-κB, which in turn destabilizes MyoD, a transcription factor that regulates muscle cell differentiation (8). Walsmith et al showed an inverse relationship between TNFα production by peripheral blood mononuclear cells (PBMCs) and body cell mass in women with RA. They found no difference in TNFα production by PBMCs between patients with RA and controls, except after stimulation with endotoxin (7). In the current study, where TNFα was measured in serum using high-sensitive ELISA, no relationship with body composition was found. In addition, there was no difference in TNFα levels between patients and controls. However, the exact pathophysiologic mechanism of muscle decay remains unknown and many other inflammatory cytokines and molecular pathways may be involved.

Of interest was the inverse relationship between CRP level and physical activity. This is in concordance with large epidemiologic studies suggesting that exercise may reduce inflammation (33,34). Given the cross-sectional nature of these studies and the current study, cause and effect cannot be determined. One might be inclined to conclude that in patients with AS, those with the lowest inflammation are better able to be physically active. However, based on our results, it can be hypothesized that higher levels of habitual physical activity result in lower plasma CRP, resulting in lower inflammation. This is supported by a study by Lund et al, showing that healthy subjects engaging in regular physical activity had lower levels of CRP than sedentary subjects. When the physically active subjects turned sedentary for 1 week and the sedentary subjects became moderately active for 1 week, plasma levels of CRP remained unaltered (35). This indicated that plasma CRP was related to habitual physical activity and not affected by short-term changes in activity behavior. On the other hand, a 10-week exercise training program did decrease CRP levels in sedentary subjects (36). These findings warrant further research into the relationship between physical activity and CRP level in patients with rheumatic inflammatory disorders.

One of the strong points about the current study is the use of accurate well-validated assessment techniques. We chose to use a 3-C model of body composition, based on deuterium dilution to assess total body water and air-displacement plethysmography to assess body volume. The 3-C model as described by Siri (16) provides accurate measures of FFM and FM with an error of $<1\%$ when compared to the gold standard 4-compartment model (body volume, total body water, and bone by DXA) (37). The major advantage over 2-compartment models is that fewer assumptions have to be made about the composition of fat-free tissue. Although the 3-C model provides an accurate measure of total body FM and FFM, the latter constitutes muscle but also bone, visceral organs, and other tissues. It would be interesting for future studies to specifically study muscle mass at a local level using MRI.

The triaxial accelerometer used has previously been validated at our laboratories (17) and was proven to be the best accelerometer available to assess daily living physical activity (12). Aerobic fitness was tested by an incremental test on a bicycle ergometer to maximal exertion, the gold standard to measure $V_{O_{2max}}$.

When patients are recruited for a study into physical activity, fitness, and body composition, there is a risk of selection bias. However, based on CRP levels and the BASDAI, it is clear that there was a wide range in disease activity. Fifty-six percent of the patients had a BASDAI score of >4 and the average BASDAI score of 4.3 indicates that the majority of the patients had active disease (38). The limitation in the study might be the small sample size. Especially when exploring the different role CRP level could have on the FFMI and physical activity in patients versus controls, we might have missed an effect due to the small sample size. A larger study is recommended to allow correction for potential confounding factors such as medication use and disease severity. It would be interesting to study body composition, physical activity, and the possible relationship with inflammation in a large group of AS patients, including those receiving anti-TNF therapy.

In conclusion, we showed that patients with AS are equally active as healthy controls. There was no evidence for a decreased FFMI in patients, and their FFMI was positively related to their level of physical activity. Despite the lack of group differences between patients and controls, subjects with higher levels of CRP had a lower FFMI, but this was not independent of physical activity. Given the relationship between physical activity, CRP level, and the FFMI, physical activity may prevent muscle loss and perhaps decrease inflammation in patients with AS, and plausibly in rheumatic inflammatory disorders in general.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Plasqui had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Plasqui, Boonen, Geusens, van der Linden.

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Analysis and interpretation of data. Plasqui, Boonen, Geusens, Kroot, Starmans, van der Linden.

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