Obesity Is Common in Axial Spondyloarthritis and Is Associated with Poor Clinical Outcome

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ABSTRACT. *Objective.* To assess the prevalence of overweight and obesity in a large cohort of patients with axial spondyloarthritis (axSpA) in comparison with the general population. To explore the relationship of body mass index (BMI) with clinical outcome in axSpA.

Methods. Patients from the Groningen Leeuwarden Axial SpA cohort who visited the outpatient clinic in 2011/2012 were included in this cross-sectional analysis. Body weight, height, disease activity, physical function, and quality of life (QoL) were assessed. Patients were divided into normal weight (BMI < 25 kg/m^2), overweight (BMI ≥ 25 to < 30 kg/m^2), and obese (BMI ≥ 30 kg/m^2). BMI data for the general population in the same demographic region, matched for age and sex, were obtained from the LifeLines Cohort Study.

Results. Of the 461 patients with axSpA, 37% were overweight and 22% were obese. In the LifeLines cohort (n = 136,577), 43% were overweight and 15% were obese. Overweight and obese patients were older, had longer symptom duration, and had more comorbidities, especially hypertension. Further, obese patients had significantly higher disease activity, worse physical function, and worse QoL than overweight and normal weight patients (mean Bath Ankylosing Spondylitis Disease Activity Index 4.5, 3.5, 3.8; mean Ankylosing Spondylitis Disease Activity Score 2.8, 2.2, 2.3; median C-reactive protein 5, 3, 3 mg/l; median erythrocyte sedimentation rate 13, 8, 8 mm/h; median Bath Ankylosing Spondylitis Functional Index 5.2, 2.9, 2.9; median Ankylosing Spondylitis QoL Questionnaire 8, 4, 5, respectively). After adjustment for potential confounders, obesity proved to be an independent predictor of worse clinical outcome.

Conclusion. In this large observational cohort study, obesity is more common in axSpA than in the general population and it is associated with worse clinical outcome. (First Release December 15 2015; J Rheumatol 2016;43:383–7; doi:10.3899/jrheum.150648)

Key Indexing Terms:
AXIAL SPONDYLOARTHRITIS   OBESITY   BODY MASS INDEX   DISEASE ACTIVITY

Axial spondyloarthritis (axSpA) is a chronic rheumatic inflammatory disease that predominantly affects the axial skeleton. Patients with axSpA can be classified into

ankylosing spondylitis (AS) and nonradiographic axSpA (nr-axSpA)[1]. The disease usually starts between 15 and 45 years of age and is characterized by inflammatory low back pain, stiffness, and reduced spinal mobility. This leads to limitations in physical functioning and may result in physical inactivity[2].

Overweight and obesity are a worldwide growing problem. The World Health Organization (WHO) defines overweight and obesity as "abnormal or excessive fat accumulation that may impair health"[3]. It is associated with metabolic and cardiovascular diseases, some malignancies, and increased mortality and morbidity[4,5]. A valid population measure of overweight and obesity is the body mass index (BMI)[3]. Individuals with a BMI between 25 and 29.9 kg/m^2 are considered overweight, and a BMI of 30 kg/m^2 or more represents obesity. Obesity is related to an increased risk for the development of rheumatic diseases, such as rheumatoid arthritis (RA) and psoriatic arthritis (PsA) with varying OR between 1.2 and 6.5[6].

In axSpA, a few studies have investigated the influence of BMI on clinical outcome. A small cross-sectional study in 46 patients with AS demonstrated that 68% of the patients were overweight or obese. These patients had more

functional limitations, higher subjective disease activity, and fewer benefits of exercise[7]. Two retrospective studies in 155 patients with AS and 170 patients with axSpA showed significantly less response to tumor necrosis factor-α (TNF-α) blocking therapy in obese patients[8,9].

The first objective of our present study was to assess the prevalence of overweight and obesity in a large cohort of patients with axSpA in comparison with an age- and sex-matched cohort of the general population in the same demographic region. The second objective was to explore the relationship of BMI with disease activity, physical function, and quality of life (QoL) in axSpA.

MATERIALS AND METHODS

Patients with axSpA. All consecutive patients from the Groningen Leeuwarden Axial SpA (GLAS) cohort who visited the outpatient clinic in 2011 or 2012 were included in our cross-sectional analysis. The GLAS cohort is a prospective, longitudinal, observational cohort study in the northern part of the Netherlands with a standardized assessment and management protocol according to the Assessment of SpondyloArthritis international Society (ASAS) and the European League Against Rheumatism recommendations[10]. All patients were over 18 years of age and fulfilled the 1984 modified New York criteria for AS (> 90% of the population)[11] or the 2009 ASAS criteria for nr-axSpA[12].

Body weight and height were measured by physical examination, and BMI was calculated (weight in kg divided by the square of height in meters). Patients were divided into 3 BMI categories according to the WHO criteria: normal weight (BMI < 25 kg/m^2), overweight (BMI ≥ 25 to < 30 kg/m^2), and obese (BMI ≥ 30 kg/m^2)[3]. Because of the small number of underweight patients (n = 8), these patients were included in the normal weight group.

Patient characteristics assessed included age; sex; symptom duration; time since diagnosis; HLA-B27 status; history of inflammatory bowel disease (IBD), uveitis, or psoriasis; presence of peripheral arthritis (defined as ≥ 1 swollen joint); entheseal involvement (defined as ≥ 1 tender enthesis based on the Maastricht AS enthesitis score 0–13); use of nonsteroidal antiinflammatory drugs (NSAID), disease-modifying antirheumatic drugs, or TNF-α blockers; and comorbidity. Patients were questioned about possible comorbidities by the physician based on the items of the self-administered comorbidity questionnaire, a validated instrument to determine comorbidity in AS[13].

Disease activity was assessed by the Bath AS Disease Activity Index (BASDAI), AS Disease Activity Score (ASDAS), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR). Physical function and QoL were assessed using the Bath AS Functional Index (BASFI) and AS quality of life questionnaire (ASQoL), respectively.

The GLAS cohort study was conducted according to the principles of the Declaration of Helsinki, approved by the local ethics committees of the Medical Center Leeuwarden and the University Medical Center Groningen (UMCG), and all patients provided written informed consent to participate in the study.

General LifeLines population. BMI data for the general population were obtained from the LifeLines Cohort Study, a large 3-generation, population-based, longitudinal cohort study in the northern part of the Netherlands with a comparable age distribution as in the GLAS cohort[14]. Between 2006 and 2013, inhabitants of the northern part of the Netherlands were invited to participate, and their weight and height were measured. The present analysis was limited to participants who were 18 years or older (n = 136,577). Because there were more women than men in the LifeLines Cohort Study, data were adjusted for the sex distribution in the GLAS cohort (men > women) by stratifying the data for sex and multiplying the prevalence rates of normal weight, overweight, and obesity with the proportion of men or women in the GLAS cohort.

The LifeLines Cohort Study was conducted according to the principles of the Declaration of Helsinki and approved by the local ethics committee of the UMCG, and all participants provided written informed consent to participate.

Statistical analysis. Results were expressed as number of patients (%), mean ± SD, or median (range) for categorical, normally distributed, and non-normally distributed data, respectively. Descriptive statistics were used to compare the prevalence of overweight and obesity in patients with axSpA with the LifeLines population. Chi-square test, 1-way ANOVA (with posthoc LSD), and Kruskal-Wallis test (with posthoc Mann-Whitney U test) were used as appropriate to analyze the relationship of BMI categories with patient characteristics and clinical outcome in patients with axSpA. Additionally, univariable and multivariable linear regression analyses were used to investigate the association between BMI or obesity and clinical outcome corrected for potential confounders [age, sex, symptom duration, HLA-B27 status, and presence of any comorbidity (yes/no), or presence of a specific comorbidity related to obesity: cardiovascular disease, hypertension (HTN), or diabetes (yes/no)]. If residuals were non-normally distributed, outcome variables were log transformed. Statistical analysis was performed with IBM SPSS Statistics 22 (SPSS). P values ≤ 0.05 were considered statistically significant.

RESULTS

In total, 461 patients with axSpA were included. The mean age was 45.3 years (SD ± 13), 66% were men, median symptom duration was 17 years (range 0–61), and 80% were HLA-B27–positive. Patients had a mean BASDAI of 3.8 ± 2.3 and a mean ASDAS 2.4 ± 1.0. History of IBD was reported in 62 patients (14%), uveitis in 146 (33%), and psoriasis in 52 (11%). Comorbidity was present in 198 patients (43%). HTN was the most frequently reported comorbidity (Table 1).

Overweight and obesity in axSpA versus the general population. The mean BMI of the patients with axSpA was 26.5 kg/m^2 (SD ± 4.6). The prevalence of overweight and obesity was 37% and 22%, respectively. Of the 100 obese patients, 19% had severe obesity (BMI ≥ 35 to < 40 kg/m^2) and 3% had morbid obesity (BMI ≥ 40 kg/m^2).

In comparison, the mean BMI of the age- and sex-matched LifeLines population was 26.1 kg/m^2 (SD ± 4.3) and the prevalence of overweight and obesity was 43% and 15%, respectively.

Relationship between BMI and clinical outcome in axSpA. Patients with axSpA who were overweight and obese were significantly older, had longer symptom duration, and had comorbidity more often, especially HTN, than patients with normal weight. Further, patients with obesity were less frequently HLA-B27–positive (Table 1).

Obese patients had significantly higher disease activity than overweight or normal weight patients in regard to BASDAI (mean 4.5, 3.5, 3.8, respectively), ASDAS (mean 2.8, 2.2, 2.3), CRP (median 5, 3, 3 mg/l), and ESR (median 13, 8, 8 mm/h). Obese patients also had significantly higher BASFI (median 5.2, 2.9, 2.9, respectively) and ASQoL (median 8, 4, 5) than overweight and normal weight patients, reflecting worse physical function and QoL (Table 1).

Univariable linear regression analysis showed that BMI and obesity were significantly associated with BASDAI, ASDAS, CRP, ESR, BASFI, and ASQoL (Table 2). After adjustment for potential confounders in multivariable linear

Table 1. Patient characteristics and clinical outcome of patients with axSpA, stratified for BMI categories. Values are n (%), mean ± SD, or median (range).

Characteristics	All Patients, n = 461	Normal Weight, < 25.0 kg/m², n = 188	Overweight, 25.0 to < 30.0 kg/m², n = 173	Obese, ≥ 30.0 kg/m², n = 100
Age, yrs	45.3 ± 12.8	40.3 ± 12.1	48.2 ± 12.4*	49.6 ±11.6*
Male	303 (66)	117 (63)	124 (72)	62 (62)
Symptom duration, yrs	17 (0–61)	13 (0–53)	20 (1–61)*	19 (0–54)*
Time since diagnosis, yrs	8 (0–54)	7 (0–41)	10 (0–48)	8 (0–54)
HLA-B27+	361 (80)	155 (84)	138 (82)	68 (69)*†
BMI, kg/m²	26.5 ± 4.6	22.3 ± 1.9	27.2 ± 1.4	33.2 ± 3.1
History of IBD	62 (14)	26 (14)	19 (11)	17 (17)
History of uveitis	146 (33)	63 (34)	55 (32)	28 (28)
History of psoriasis	52 (11)	16 (9)	23 (13)	13 (13)
Presence of peripheral arthritis	16 (4)	9 (5)	4 (2)	3 (3)
Presence of entheseal involvement	160 (36)	63 (35)	57 (34)	40 (42)
NSAID use	228 (50)	94 (50)	80 (46)	54 (54)
DMARD use	32 (7)	16 (9)	10 (6)	6 (6)
TNF-α inhibitor use	204 (44)	79 (42)	84 (49)	41 (41)
Comorbidity	198 (43)	55 (30)	82 (48)*	61 (62)*†
CVD	35 (8)	10 (5)	14 (8)	11 (11)
Hypertension	105 (23)	15 (8)	45 (26)*	45 (45)*†
Diabetes	16 (4)	3 (2)	6 (4)	7 (7)
Lung disease	28 (6)	8 (4)	11 (6)	9 (9)
Ulcer/stomach disease	5 (1)	1 (1)	3 (2)	1 (1)
Kidney disease	5 (1)	2 (1)	2 (1)	1 (1)
Liver disease	3 (1)	1 (1)	1 (1)	1 (1)
Anemia/blood disease	6 (1)	3 (2)	2 (1)	1 (1)
Cancer	6 (1)	4 (2)	1 (1)	1 (1)
Depression	12 (3)	7 (4)	3 (3)	3 (3)
OA or FM	20 (4)	7 (4)	7 (4)	6 (6)
Noninflammatory back pain	6 (1)	2 (1)	4 (2)	0 (0)
Other chronic rheumatic disease	10 (2)	3 (2)	5 (3)	2 (2)
Other‡	62 (13)	14 (7)	30 (17)*	18 (18)*
BASDAI, 0–10	3.8 ± 2.3	3.8 ± 2.3	3.5 ± 2.1	4.5 ± 2.3*†
ASDAS	2.4 ± 1.0	2.3 ± 1.0	2.2 ± 0.8	2.8 ± 1.1*†
CRP, mg/l	3 (0–94)	3 (0–73)	3 (1–94)	5 (1–82)*†
ESR, mm/h	9 (1–79)	8 (1–71)	8 (2–79)	13 (2–66)*†
BASFI, 0–10	3.3 (0–9.9)	2.9 (0–9.1)	2.9 (0–9.9)	5.2 (0.1–9.7)*†
ASQoL, 0–18	6 (0–18)	5 (0–17)	4 (0–17)	8 (0–18)*†

‡ Irritable bowel syndrome, other eye/skin problems, headache, thyroid problems, allergy, and osteoporosis. * P values ≤ 0.05 compared with patients with normal weight. † P values ≤ 0.05 compared with patients with overweight. axSpA: axial spondyloarthritis; BMI: body mass index; IBD: inflammatory bowel disease; NSAID: nonsteroidal antiinflammatory drug; DMARD: disease-modifying antirheumatic drug; TNF-α: tumor necrosis factor-α; CVD: cardiovascular disease; OA: osteoarthritis; FM: fibromyalgia syndrome; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; BASFI: Bath Ankylosing Spondylitis Functional Index; ASQoL: Ankylosing Spondylitis Quality of Life questionnaire.

regression analysis, obesity proved to be an independent predictor of higher disease activity, worse physical function, and worse QoL (Table 2).

In total, 31 obese patients had very high disease activity (BASDAI ≥ 6 and/or ASDAS > 3.5). Of these patients, 6 were treated with TNF-α blockers, 6 fulfilled the ASAS criteria and were going to start TNF-α blocking therapy, 7 had discontinued the treatment because of inefficacy or adverse events, 5 had contraindications to TNF-α blockers, and 7 did not start the therapy because of their own choice (n = 2) or expert opinion (n = 5).

DISCUSSION

Our cross-sectional analysis in a large cohort of patients with axSpA showed that more than half of the patients were overweight or obese. Obesity was present in 22% and these patients had significantly higher disease activity, worse physical function, and worse QoL.

The high prevalence of overweight and obesity in the GLAS cohort is in accordance with smaller studies in AS with comparable age and disease duration. A retrospective study in 155 patients and a cross-sectional study in 46 patients found overweight in 35% and 37%, and obesity in 25% and 31% of the patients, respectively[7,8].

The percentage of patients with axSpA who were overweight or obese was comparable to the LifeLines population (59% vs 58%), but obesity alone was more common in patients with axSpA (22% vs 15%). Obesity was

Table 2. Univariable and multivariable linear regression analysis of the association between BMI and obesity with clinical outcome.

Dependent Variables	Predicting Variables	Univariable Analysis, B (95% CI)	p	Multivariable Analysis*, B (95% CI)	p
BASDAI	BMI	0.056 (0.011–0.101)	0.014	0.047 (–0.004–0.099)	0.072
	Obesity	0.841 (0.341–1.341)	0.001	0.629 (0.080–1.179)	0.025
ASDAS	BMI	0.036 (0.016–0.057)	< 0.001	0.033 (0.010–0.057)	0.005
	Obesity	0.526 (0.299–0.752)	< 0.001	0.497 (0.248–0.746)	< 0.001
CRP (log)	BMI	0.015 (0.006–0.023)	0.001	0.017 (0.007–0.026)	0.001
	Obesity	0.186 (0.092–0.279)	< 0.001	0.231 (0.130–0.333)	< 0.001
ESR (log)	BMI	0.013 (0.005–0.021)	0.003	0.013 (0.003–0.022)	0.009
	Obesity	0.116 (0.020–0.211)	0.017	0.118 (0.015–0.220)	0.024
BASFI	BMI	0.133 (0.083–0.183)	< 0.001	0.073 (0.019–0.128)	0.009
	Obesity	1.609 (1.056–2.163)	< 0.001	1.040 (0.460–1.619)	< 0.001
ASQoL	BMI	0.147 (0.042–0.252)	0.006	0.086 (–0.031–0.204)	0.150
	Obesity	2.891 (1.744–4.038)	< 0.001	2.157 (0.878–3.435)	0.001

* Adjusted for age, sex, symptom duration, HLA-B27 status, and comorbidity. BMI: body mass index; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; BASFI: Bath Ankylosing Spondylitis Functional Index; ASQoL: Ankylosing Spondylitis Quality of Life questionnaire.

also more common in our axSpA cohort than in the general Dutch and worldwide adult population, in which the prevalence of obesity has been estimated to be 11–13%[3,15]. In line with our data, higher prevalence rates of obesity in comparison with the general population were also found in patients with RA, psoriasis, and PsA[16,17]. These data underline that obesity especially seems to be more common in rheumatic diseases, including axSpA, than in the general population.

In our study, obese patients were older, had comorbidities more often, especially HTN, and were less frequently HLA-B27–positive. A significantly lower presence of HLA-B27 positivity in obese patients was also found in a previous retrospective study of 155 patients with AS[8]. It has been suggested that obesity contributes to the pathogenesis and inflammatory processes of several inflammatory diseases such as RA and PsA[6]. Our findings also suggest an association between obesity and axSpA without the presence of HLA-B27. Because we performed a cross-sectional analysis, no statements can be made about causality.

Obese patients with axSpA had higher disease activity according to both subjective and objective disease activity assessments (BASDAI, ASDAS, CRP, ESR), and experienced worse physical function and QoL assessed with questionnaires (BASFI and ASQoL) than overweight and normal weight patients. Higher subjective measures of disease activity [BASDAI, visual analog scale (VAS) patient global score] and worse physical function (BASFI) were also found in obese patients with AS in a small cross-sectional study[7]. Obesity is found to be associated with an abnormal accumulation of adipose tissue and it is suggested that white adipose tissue is an active endocrine organ that secretes adipocytokines or adipokines (e.g., TNF-α), which may be responsible for a proinflammatory state in obese subjects[6,18].

Despite a higher disease activity, obese patients in our study did not use TNF-α blockers more often. Our exploratory analyses in relatively small subgroups suggest that discontinuation of TNF-α blocking therapy attributable to inefficacy or adverse events and contraindications to this treatment were relatively common in obese patients with very high disease activity. These results imply that it is difficult to treat obese patients adequately.

In addition, previous studies have shown that obesity is a negative predictor of treatment response[8,9]. A retrospective study in 155 patients with AS showed that obese patients had a significantly lower treatment response, defined as 50% improvement in BASDAI, VAS, and CRP after 6 months of infliximab therapy compared with baseline than normal weight patients (27% vs 78%, 17% vs 73%, and 39% vs 88%, respectively)[8]. Another study of 170 patients with axSpA demonstrated a significantly lower proportion of patients reaching BASDAI50 response after 12 months of TNF-α blocking therapy (infliximab, etanercept, adalimumab) in obese than in normal weight patients (30% vs 73%)[9]. These associations between obesity, disease activity, and treatment response were also found in RA and PsA, and suggest that obesity is involved in the response to TNF-α blocking therapy[6]. It has been found that the response to TNF-α blockers is related to the volume of distribution of these agents, which could be influenced by overweight and obesity[19]. In a previous study in patients with PsA, weight loss was associated with an improved response to TNF-α blocking therapy[20]. However, the exact interactions between obesity and disease pathways in axSpA and other rheumatic diseases still remain unclear[21].

On the other hand, physical and functional limitations related to obesity itself or due to high disease activity can result in physical inactivity, which successively may lead to weight gain. Physical exercise is important in the management of axSpA to maintain physical function and to reduce symptoms, but it is also recommended to prevent obesity[22]. Besides medication use to reduce symptoms

related to disease activity, such as NSAID and/or TNF-α blocking therapy, physical exercise seems important to break the vicious circle between disease activity, physical inactivity, and obesity. Unfortunately, data about physical activity were not available in our cohort.

To our knowledge, the present study was the first to investigate the prevalence of overweight and obesity in a large cohort of patients with axSpA in comparison with a large age- and sex-matched cohort of the general population in the same demographic region. In our study, BMI categories were used. BMI does not consider the abdominal fat distribution, while anthropometric measures such as waist circumference better reflect the amount of abdominal adipose tissue[23]. However, BMI is a valid and easily evaluable assessment in clinical practice and it is the most useful population-level measure to assess absolute fat mass adjusted for body height[3].

Obesity seems to be more common in patients with axSpA than in the general population. Obesity in axSpA was an independent predictor of both higher subjective and objective assessments of disease activity and worse physical function and QoL. Clinicians and patients should be aware of the negative consequences of being obese with axSpA, and if possible, adjustments in treatment options and regimens should be made. Our results underline the need for studies investigating the pathophysiological mechanisms of body fat in relation to inflammation in axSpA. Further, prospective data may clarify the relationships among obesity, disease activity, and physical function and the influence of weight loss and physical activity on clinical outcome in axSpA.

ACKNOWLEDGMENT

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