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Analysis of Disease Activity in Axial Spondyloarthritis Reveals that the Obesity-Activity Association Could Vary Depending on the Activity Index Chosen for This Purpose

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Abstract: Background and aims: Obesity has been related to increased disease activity in axial spondyloarthritis (axSpA), but this association might vary depending on the composite index chosen to assess disease activity. We aim to check that possibility. Methods: Three hundred and thirty consecutive patients were recruited from the monographic axSpA unit of a university center. To assess disease activity, BASDAI and ASDAS-CRP measurements were collected. The factors associated with the different disease activity thresholds of these instruments were analyzed using univariate and multivariate logistic regression models. Results: The study included 127 women and 203 men, mean age 47.6 (SD 12.9) years, median disease duration 8 years [IQR: 4-16], and 63% on biologic therapies. Most patients met therapeutic goals with a BASDAI < 4 in 187 (56.7%) and ASDAS inactive/low category in 182 (55.2%). Being male was associated with BASDAI remission (OR 2.63), but smoking reduced this likelihood (OR 0.28). Similar findings were found for ASDAS inactive disease (male: OR 2.09; smoking: OR 0.39). The variables associated with BASDAI ≥ 4 in the multivariate logistic model were male (OR 0.36), age (OR 1.02), smoking (OR 2.39), and obesity (OR 2.94), whereas associations with active/very active ASDAS categories were male (OR 0.49), age (OR 1.02), and smoking (OR 2.34). However, obesity was not associated with these higher ASDAS categories (p = 0.183). Conclusions: While the association between smoking and increased disease activity was consistent across all composite activity indices, the obesity-activity relationship was only apparent through the BASDAI.

Keywords: obesity; smoking; ASDAS; BASDAI; axial spondyloarthritis; disease activity

1. Introduction

Spondyloarthritis (SpA) is a group of chronic inflammatory processes with a predilection for the axial skeleton and a common pathogenic and genetic architecture. Within the predominantly axial forms, radiographic forms (the former ankylosing spondylitis) and non-radiographic forms are distinguished, but both entail a serious functional impairment and a decrease in the quality of life for affected patients [1].

Although there are different ways of approaching the estimation of the activity and impact that these diseases generate, the two most commonly used composite indices to assess disease activity are the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Ankylosing Spondylitis Disease Activity Score (ASDAS), the latter being a derivation of the former that incorporates objective parameters such as C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR) [2]. Currently,

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the Assessment of Spondyloarthritis International Society (ASAS) group recommends the ASDAS-CRP for the estimation of activity, monitoring of response to treatment, and selection of patients for advanced therapies [3].

Cardiometabolic comorbidity is a common companion of SpA, but there are differences in the prevalence of these factors across different SpA phenotypes. Thus, for example, traditional cardiometabolic risk factors tend to be more prevalent in patients with psoriatic arthritis (PsA) than in axial SpA (axSpA), with the exception of smoking, which is more much prevalent in the latter [4–6]. The relevance of this association lies not only in an increased cardiovascular risk, but in the known link between some of these factors and increased activity, poorer functioning, structural damage, and poorer persistence of treatments, especially biological ones, in patients with SpA [6–10]. In this sense, the two factors most consistently linked to these adverse outcomes are obesity and smoking.

However, one aspect that has not been fully clarified in the literature of recent years is to analyze whether the association between these factors (mainly tobacco and obesity) and a greater inflammatory activity is partially skewed by the particular instrument used to estimate such activity. In fact, some aspects included in the BASDAI, such as fatigue and entheseal pain, are not included in the ASDAS, and it is known that obese patients may report more fatigue and pain than non-obese [11,12]. Although there is usually a direct link between fatigue, pain, and inflammation in SpA, fatigue and pain may be multifactorial disease domains not necessarily associated with inflammatory activity in all circumstances [13,14]. Therefore, given the existence of differences in the individual components that make up each instrument for measuring SpA disease activity, it is plausible that factors such as obesity or tobacco may show correlations with greater disease activity when such a link is measured with one instrument, and, however, no such association may be found when the measurement tool chosen is another. In an attempt to elucidate these assumptions, the present study which includes a significant number of patients with axSpA, was approached with these premises in mind.

2. Materials and Methods

2.1. Study Population

For the purposes of this observational cross-sectional study, 330 consecutive patients who met ASAS criteria for axSpA were included [15]. Patients were recruited from a monographic axSpA unit of a university center in a northwestern Spain region (total population of one million inhabitants). All patients were of both sexes and over 18 years old. The recruitment period extended from January to October 2023. These patients are seen every 3 months when they start systemic therapy or when they have poor symptomatic control, or every 6 months when they progress satisfactorily, reaching treatment goals (ASDAS remission or low disease activity). The baseline and follow-up protocol are the same for all patients. The work procedures of this SpA unit are regularly audited and currently have the advanced quality seal awarded by the Spanish Society for Healthcare Quality. All patients were informed of the objectives of the study and all signed an informed consent to participate. This study was conducted in full conformance with the Spanish SAS Order/3470/2009 of the Ministry of Health and Social Policy, local laws and regulations, and the ethical principles laid down in the Declaration of Helsinki. Compliance with the provisions of the new Regulation (EU) 2016/679 of the European Parliament and the Council of 27 April 2016 on Data Protection (GRDP) was also ensured.

2.2. Study Variables

Socio-demographic aspects, lifestyles, and previous medical history were recorded. The following variables were also collected: age at onset, symptoms duration, family history of disease, comorbid factors (including components of the metabolic syndrome such as diabetes, hypertension, dyslipidemia and obesity), axial and peripheral clinical manifestations, number of painful joints, number of inflamed joints, enthesitis, dactylitis, co-manifestations (uveitis, psoriasis, inflammatory bowel disease). Standard disease metrology included: disease activity according to the BASDAI and the ASDAS-CRP, physical function according to the Bath Ankylosing Spondylitis Functional Index

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(BASFI), and the general disease impact according to the ASAS-Health Index (ASAS HI) questionnaire. We have previously contrasted the validity, correlations, and feasibility of all these standard measures in our clinical setting [16–18]. Pelvis radiographs were performed in anteroposterior projection, as well as anteroposterior and lateral views of the cervical and lumbar spine. The degree of involvement of the sacroiliac joints was assessed by the New York (NY) criteria [19]. However, no specific method of structural damage reading was chosen, while the imaging features of axSpA were simply recorded (sacroiliitis, syndesmophytes, vertebral squaring). Current and past medication in relation to axSpA (NSAIDs, conventional DMARDs, biologic and targeted-specific DMARDs) and the pertinent analytical parameters such as HLA-B27 (only at baseline), ESR, and CRP, were also collected.

2.3. Statistical Methodology

A descriptive statistical study of all the variables was made, using central and dispersion measures for the quantitative variables, as well as absolute and relative frequencies for the qualitative ones. Variables were compared by parametric and non-parametric statistical tests depending on whether their distribution was normal or not. Comparisons in the study population based on sex (males versus females) and on the presence of HLA B27 (positive versus negative) were also included. For the purposes of this study, we used the following cut-off thresholds: BASDAI remission (≤2), active BASDAI (≥4), ASDAS inactive disease (<1.3) and ASDAS high/very high disease activity (≥2.1). To estimate the determinants of BASDAI remission, active BASDAI, ASDAS inactive disease, and high/very high ASDAS activity categories, univariate and multivariate logistic regression models were used. The strength of the association between the variables included in the regression models and the different clinical activity thresholds was measured by odds ratio -OR- values with their 95% confidence intervals (CI). The threshold for statistical significance was set at $p < 0.05$. Data were analyzed using R software (4.3.1 "Beagle Scouts").

3. Results

3.1. Summary of Study Population

A total of 127 (38.5%) women and 203 (61.5%) men were included, mean age of 47.6 (SD 12.9) years and median disease duration of 8 years [IQR 4-16]. At the time of inclusion, 209 (63.3%) patients were receiving biological therapies, mostly anti-TNF. Most patients were under acceptable disease control with a mean BASDAI of 3.64 (SD 2.43) and a mean ASDAS of 2.07 (SD 0.852). HLA-B27 determination was positive in 227 (70.7%) patients. Most patients had radiographic axSpA (80%) with a 2.6:1 ratio favoring men. Table 1 summarizes the characteristics of the study population.

Table 1. Disease characteristics of the study population.

Features	N = 330
Age, yrs, mean (SD)	47.6 (12.9)
Disease duration, yrs, median (IQR)	8 [4-16]
Men, n (%)	203 (61.5)
Women, n (%)	127 (38.5)
Radiographic axSpA, n (%)	264 (80)

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Peripheral involvement, n (%)	60 (18.1)
SpA family history, n (%)	82 (24.8)
Educational level, n (%)	
Primary	87 (26.4)
Secondary	157 (47.6)
University	86 (26.1)
Smokers, n (%)	115 (34.8)
Obesity, BMI ≥ 30, n (%)	40 (12.1)
SpA-related conditions, n (%)	
Enthesitis	33 (10)
Anterior uveítis	56 (17)
Inflammatory bowel disease	34 (10.3)
Lab. Variables	
ESR (median, IQR), mm/h	5 [2-10.8]
CRP (median, IQR), mg/dl	0.30 [0.10-1.10]
HLA-B27, n (%)	227 (70.7)
Treatment	
NSAIDs, n (%)	233 (70.6)
Conventional DMARDs, n (%)	57 (17.3)
Oral glucocorticoids, n (%)	16 (4.8)
Biological DMARDs, n (%)	209 (63.3)

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Composite indices	
BASDAI, mean ± SD	3.64 (2.43)
BASFI, mean ± SD	3.19 (2.43)
ASDAS-CRP, mean ± SD	2.07 (0.85)
ASAS-HI, mean ± SD, n: 200	5.39 (4.0)
Outcomes*	
BASDAI remission (≤2), n (%).	99 (30)
Active BASDAI (≥4), n (%)	143 (43.3)
ASDAS inactive disease (<1.3), n (%)	70 (21.3)
ASDAS high (≥2.1-3.5), n (%)	129 (39.2)
ASDAS very high (>3.5), n (%)	18 (5.5)
ASAS HI high impact (>5), n: 200 (%)	108 (54)

yrs: years; SD: standard deviation; axSpA: axial spondyloarthritis; BMI: body mass index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; HLA: human leukocyte antigen; NSAIDs: non-steroidal anti-inflammatory drugs; DMARDs: disease-modifying anti-rheumatic drugs; BASDAI: Bath ankylosing spondylitis disease activity index; BASFI: Bath ankylosing spondylitis functional index; ASDAS: ankylosing spondylitis disease activity score; ASAS-HI: assessment of spondyloarthritis international society-health index. * The overall weighted Kappa index between ASDAS and BASDAI was 0.65 (95%IC: 0.59 - 0.71), indicating substantial agreement between both indices.

3.2. Differences Based on Sex

Men showed a significantly longer disease duration [median 10 (IQR 5-20) years] than women [median 6 (IQR 3-12) years], $p < 0.001$. The female population had significantly more active disease according to BASDAI (4.37 ± 2.41 versus 3.18 ± 2.33, $p < 0.001$) and ASDAS (2.25 ± 0.78 versus 1.97 ± 0.88, $p < 0.001$). They also showed poorer functioning according to BASFI (3.52 ± 2.36 versus 2.98 ± 2.45, $p = 0.031$). In contrast, men had a higher frequency of advanced bilateral sacroiliitis (93% versus 77%, $p < 0.001$) and a higher frequency of syndesmophytes (37% versus 14%, $p < 0.001$). Regarding the analytical determinations, women had a higher ESR [median 8 (IQR 3-17) versus 4 (IQR 2- 8), $p < 0.001$]. A trend bordering on statistical significance was observed in the distribution of HLA-B27 (men: 74.6% versus women: 64.5%, $p = 0.07$).

3.3. Differences Based on HLA-B27

At the time of inclusion, patients with HLA-B27 were younger (46.3 ± 13.1 years versus 49.9 ± 11.8 years, $p = 0.016$) and had a longer disease duration [median 9.50 (IQR 4-, 19.3) years versus 6 (IQR 3-11) years, $p = 0.003$]. The percentage of NSAID users was higher among HLA-B27-positive

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individuals (75.3% versus 61.7%, p = 0.02). Regarding extra-musculoskeletal manifestations, HLA-B27-positive patients had a higher prevalence of uveitis (19.4% versus 6.4%, p = 0.006), but HLA-B27-negative patients had more inflammatory bowel disease (21.3% versus 5.3%, p < 0.001). HLA-B27-negative subjects had significantly higher mean BASDAI (4.26 ± 2.42 versus 3.45 ± 2.39, p = 0.006) and ASDAS values (2.21 ± 0.81 versus 2.03 ± 0.87, p = 0.035) than B27-positive subjects. Regarding the distribution of cardiometabolic factors, HLA-B27 patients showed a lower diabetes prevalence (2.6% versus 7.4%, p = 0.06). The prevalence of bilateral sacroiliitis was higher among HLA-B27-positive patients (92% versus 74.5%, p < 0.001).

3.4. Factors Associated with BASDAI Remission (≤2)

In the univariate logistic regression model, BASDAI remission was significantly associated with being male (OR 2.34, p = 0.001), NSAIDs intake (OR 0.35, p < 0.001), smoking (OR 0.33, p < 0.001), ASDAS (OR 0.04. p < 0.001), BASFI (OR 0.39, p < 0.001), and HLA-B27 positivity (OR 2.04, p = 0.017). In the multivariate logistic regression model the associated factors were male [OR 2.63, 95%CI: 1.45-4.91, p = 0.002] and smoking [OR 0.28, 95%CI: 0.15-0.53, p < 0.0001].

3.5. Factors Associated with ASDAS Inactive Disease (<1.3)

In the univariate logistic regression model, the ASDAS inactive disease category was significantly associated with being male (OR 1.99, p = 0.03), age (OR 0.97, p = 0.022), NSAIDs (OR 0.22, p < 0.001), smoking (OR 0.40, p = 0.008), BASDAI (OR 0.22, p < 0.001), BASFI (OR 0.26, p < 0.001), CRP (OR 0.70, p = 0.031), and sacroiliitis (OR 3.41, p = 0.047). The associated factors in the multivariate model were male [OR 2.1, 95%CI: 1.07-4.26, p = 0.036] and smoking [OR 0.39, 95%CI: 0.18-0.79, p = 0.012].

3.6. Factors Associated with Active BASDAI (≥4)

In the univariate model, associated variables were male (OR 0.40, p < 0.001), NSAIDs (OR 1.85, p = 0.015), uveitis (OR 0.43, p = 0.011), obesity (OR 2.3, p = 0.017), smoking (OR 2.04, p = 0.002), ASDAS (OR 20.4, p < 0.001), BASFI (OR 2.8, p < 0.001), ESR (OR 1.03, p = 0.021), HLA-B27 positive (OR 0.49, p = 0.004), and sacroiliitis (OR 0.45, p = 0.016). Significant factors in multivariate regression were male [OR 0.36, 95%CI: 0.21-0.62, p < 0.0001], age [OR 1.03, 95%CI: 1.00-1.05, p = 0.028], smoking [OR 2.39, 95%CI: 1.40-4.12, p = 0.001], and obesity [OR 2.94, 95%CI: 1.26-7.16, p = 0.014]. Table 2 displays full data included in univariate and multivariate models.

Table 2. Full regression model for active BASDAI.

Univariate regression model OR (95%CI), p-value	Multivariate regression model OR (95%CI), p-value
Male 0.38 (0.24, 0.61), <0.001	**Male** **0.36 (0.20, 0.61), < 0.0001**
Age 1.01 (0.99, 1.03), 0.069	**Age** **1.02 (1.00, 1.05), 0.028**
Educational level Secondary: 0.90 (0.53, 1.52), 0.703 University: 0.66 (0.36, 1.22), 0.187	
Disease duration 0.97 (0.95, 1.00), 0.101	Disease duration 0.98 (0.94, 1.01), 0.232
Enthesitis 1.33 (0.60, 2.98), 0.476	
NSAID	

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1.84 (1.12, 3.03), 0.015	
Biologic DMARDs 1.26 (0.80, 1.99), 0.307	Biologic DMARDs 1.06 (0.62, 1.83), 0.810
Conventional DMARDs 1.31 (0.74, 2.33), 0.344	
Uveitis 0.42 (0.22, 0.82), 0.011	
IBD 2.00 (0.97, 4.13), 0.058	
Diabetes 2.02 (0.70, 5.83), 0.190	
Hypertension 1.30 (0.70, 2.41), 0.403	
Obesity 2.31 (1.16, 4.59), 0.017	**Obesity** **2.94 (1.26, 7.15), 0.014**
Smoking 2.04 (1.29, 3.23), 0.002	**Smoking** **2.39 (1.40, 4.12), 0.001**
ASDAS 20.39 (10.64, 39.09), <0.001	
BASFI 2.75 (2.24, 3.38), <0.001	
ESR 1.02 (1.00, 1.05), 0.021	
CRP 1.05 (0.98, 1.12), 0.135	
HLA-B27 0.49 (0.30, 0.79), 0.004	HLA-B27 0.58 (0.32, 1.04), 0.069
Sacroiliitis 0.44 (0.23, 0.85), 0.016	
Syndesmophytes 1.17 (0.72, 1.90), 0.505	

BASDAI: Bath Ankylosing Spondylitis Disease Activity Score; OR: Odds Ratio; CI: Confidence Interval; NSAID: Non-Steroidal Anti-Inflammatory Drugs; DMARDs: Disease Modifying Anti-Rheumatic Drugs; IBD: Inflammatory Bowel Disease; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASFI: Bath Ankylosing Spondylitis Functional Index; ESR: Erythrocyte Sedimentation Rate; CRP: C-Reactive Protein; HLA: Human Leukocyte Antigen. Significant associations in the multivariate model are highlighted in bold.

3.7. Factors Associated with High/Very High ASDAS (≥ 2.1)

In the univariate logistic model, the following significant relationships were found: male (OR 0.48, p = 0.001), university degree (OR 0.49, p = 0.022), NSAID (OR 2.6, p < 0.001), uveitis (OR 0.51, p = 0.04), smoking (OR 2.2, p = 0.001), BASDAI (OR 2.6, p < 0.001), BASFI (OR 2.2, p < 0.001), ESR (OR 1.04, p = 0.001), CRP (OR 1.15, p = 0.002), HLA-B27 positive (OR 0.57, p = 0.021). In the multivariate model, the following variables stood out: male [OR 0.49, 95%CI: 0.29-0.83, p = 0.008], age [OR 1.02,

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95%CI: 1.00-1.05, p = 0.039], and smoking [OR 2.34, 95%CI: 1.39-3.98, p = 0.001]. Table 3 shows full data included in univariate and multivariate models.

Table 3. Full regression model for the higher ASDAS categories.

Univariate regression model OR (95%CI), p-value	Multivariate regression model OR (95%CI), p-value
Male 0.48 (0.30, 0.75), 0.001	**Male** **0.48 (0.28, 0.82), 0.008**
Age 1.01 (0.99, 1.03), 0.226	**Age** **1.02 (1.00, 1.04), 0.039**
Educational level Secondary: 0.60 (0.36, 1.02), 0.062 University: 0.49 (0.26, 0.90), 0.022	
Disease duration 0.98 (0.95, 1.00), 0.120	Disease duration 0.97 (0.94, 1.00), 0.077
Enthesitis 0.75 (0.33, 1.72), 0.507	
NSAID 2.59 (1.56, 4.31), <0.001	
Biologic DMARDs 1.45 (0.92, 2.29), 0.105	Biologic DMARDs 1.37 (0.81, 2.32), 0.238
Conventional DMARDs 1.23 (0.69, 2.18), 0.473	
Uveitis 0.51 (0.27, 0.97), 0.040	
IBD 1.55 (0.75, 3.20), 0.232	
Diabetes 1.08 (0.38, 3.07), 0.874	
Hypertension 0.81 (0.43, 1.53), 0.527	
Obesity 1.92 (0.97, 3.79), 0.059	Obesity 1.74 (0.77, 4.02), 0.183
Smoking 2.15 (1.35, 3.41), 0.001	**Smoking** **2.34 (1.39, 3.97), 0.001**
BASDAI 2.60 (2.14, 3.17), <0.001	
BASFI 2.16 (1.84, 2.53), <0.001	
ESR 1.04 (1.01, 1.07), 0.001	
CRP 1.14 (1.05, 1.25), 0.002	

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HLA-B27 0.56 (0.34, 0.91), 0.021	HLA-B27 0.76 (0.43, 1.35), 0.360
Sacroiliitis 0.66 (0.34, 1.25), 0.206	
Syndesmophytes 1.09 (0.67, 1.76), 0.722	

ASDAS: Ankylosing Spondylitis Disease Activity Score; OR: Odds Ratio; CI: Confidence Interval; NSAID: Non-Steroidal Anti-Inflammatory Drugs; DMARDs: Disease Modifying Anti-Rheumatic Drugs; IBD: Inflammatory Bowel Disease; BASDAI: Bath Ankylosing Spondylitis Disease Activity Score; BASFI: Bath Ankylosing Spondylitis Functional Index; ESR: Erythrocyte Sedimentation Rate; CRP: C-Reactive Protein; HLA: Human Leukocyte Antigen. Significant associations in the multivariate model are highlighted in bold.

4. Discussion

In the present observational study, which included a large sample of patients treated in the axSpA monographic unit from a university center, we have confirmed some classic findings such as that men are more likely to achieve stringent treatment goals such as BASDAI remission and ASDAS inactive disease, or the fact that smoking significantly hinders these goals. In addition, both findings were independent of exposure to biological therapies in this study. On the other hand, both smoking (OR 2.39) and obesity (OR 2.94) were associated with BASDAI active disease, while this association was only maintained for the first of these factors (OR 2.34) when the activity assessment tool used was the ASDAS, disappearing such a link in the case of obesity.

Our observations seem to strongly support the role of tobacco in terms of increased inflammatory activity in axSpA. In fact, we not only found that tobacco hampers the achievement of treatment goals such as inactive disease according to ASDAS or remission according to BASDAI, but it was significantly associated with the possibility of active or very active disease according to both measurement instruments. On the other hand, we also found an association between active smoking and structural damage with an OR 1.9 (95%CI: 1.01-3.74, $p < 0.05$) for syndesmophyte formation (data not shown). All this has also been clearly reflected by other studies [20–22]. For example, in a meta-analysis of axSpA cross-sectional studies, ever smokers had significantly higher BASDAI, BASFI and spinal pain, and higher impact on quality of life than never smokers [21]. Also, in another large survey, respondents with PsA ever smokers reported poorer quality of life, global health, pain, and fatigue than never smokers [22]. The strength of this relationship is also supported by the fact that the strong link between inflammatory activity and smoking is captured regardless of the instrument used to measure disease activity, as we confirmed here.

The story regarding the activity-obesity relationship in axSpA is somewhat different when compared to the same relationship for smoking. Thus, although some studies, including meta-analyses, point to a positive correlation between higher BMI and increased disease activity and other adverse outcomes, not all studies suggest the same [4–10,23–25]. In fact, the distribution of this comorbidity is very different across different SpA phenotypes. In that line, the relationship between obesity and the risk of PsA is very strongly supported, and currently obesity is considered one of the key factors in the long-term risk for the development of PsA among psoriasis patients [26]. Furthermore, the prevalence of obesity in PsA is significantly higher than that observed in axSpA [6,12]. Anyway, the mechanisms through which obesity or overweight could influence disease activity in axSpA are manifold. First, adipose tissue is not only an energy reservoir, but also the source of a host of cytokines and proinflammatory mediators that determine a chronic low-grade inflammatory state [27]. Moreover, many of these proinflammatory pathways are also shared with SpA [27]. Second, according to the pathogenetic theory of the entheseal organ, the mechanical overload caused by overweight and obesity may be the starting point of a mechanical stress-linked aberrant immune response driven by enthesis-resident innate immune lineages [10,28]. These responses under certain genetic conditioning can become chronic, giving rise to an overactivated osteo-reparative mechanism on the bone and entheses [10]. Finally, the increased risk of developing

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osteoarthritis among obese subjects [29], or even other much less studied factors such as the interplay between breastfeeding, gut dysbiosis, obesity and the disease [30], would add to an extremely complex network of interactions when it comes to interpreting the effect of obesity on the composite indices designed to assess disease activity.

Given the above, it is not surprising to find disparate associative lines in the different studies published so far that analyze whether or not obese patients with axSpA have a higher inflammatory burden, which in turn could translate into higher values of the composite activity indices. To resolve this question, Ortolan *et al*., performed a systematic review and meta-analysis to investigate whether overweight and obesity were associated with higher scores in BASDAI and ASDAS in axSpA adult patients. Random-effects meta-analysis was used to pool results, which were expressed as the mean difference (MD) in BASDAI and ASDAS across BMI groups. The MD in BASDAI between normal BMI and obese patients was – 0.78 ($p < 0.0001$). For ASDAS, the MD between normal BMI and obesity was – 0.42 ($p < 0.0001$). The authors concluded that the differences in terms of increased activity were only significant when comparing obese patients against normal weight, with the effect size of such differences being much more marked with the BASDAI than with the ASDAS [31]. In our study, despite the substantial agreement between both indices (weighted kappa 0.65, Table 1), obese patients were almost three times more likely to score a high BASDAI, while no relationship with the higher ASDAS categories was found. Taking this into account, along with the findings of the aforementioned meta-analysis, it appears that axSpA obese patients tend to score higher on the BASDAI compared to the ASDAS.

The reasons why obese patients score higher on the BASDAI than on the ASDAS remain speculative. The first thing to consider is that the BASDAI is a 6-item instrument, completely subjective, without any weighting by item, while the ASDAS is a tool derived from the former, but formulated logarithmically for a different weighting depending on the item, and with objective elements such as CRP and ESR [2]. Second, the lack of correctors for each item, together with a potential circularity between some of them, could lead to overestimations of the activity when the tool chosen for this purpose is BASDAI. On the other side, ASDAS combines five disease activity variables with only partial overlap, resulting in one single score with better truth (validity), enhanced discriminative capacity and improved sensitivity to change as compared to single-item variables [2]. Third, the BASDAI contains two items (fatigue and pain over enthesis points) not present in the ASDAS. We should consider that obese patients may experience fatigue and/or entheseal pain due to non-inflammatory causes, which may thus overestimate the overall BASDAI scoring. For example, in the study by Bindesbøll *et al*., obese patients reported significantly higher scores on all six questions of the BASDAI scale compared to normal or underweight patients. However, the item with the highest scoring was the one referring to fatigue with a mean of 6.64 out of 10 [32]. Unfortunately, study authors did not employ the ASDAS, thus preventing a comparative analysis. Finally, it should be mentioned that the close correlations between BMI, pain, fatigue and psycho-emotional burden could influence the scoring of the different components of the BASDAI, which could in turn be another source of overestimation of the score [11,33,34]. That said, the findings implicit in our study have an obvious translation into practice, since in axSpA obese patients the instrument for measuring disease activity should be the ASDAS rather than the BASDAI. Of course, the BASDAI will continue to be a first-rate tool in all other areas relevant to the disease.

The weaknesses of this study are of different kinds. Firstly, those typical of any cross-sectional study where the direction of the relationships, whether causal or otherwise, are impossible to establish. Secondly, the prevalence of obesity in our setting (12%) is at the lower limit of the prevalence rates previously published in this field [35]. Furthermore, although we developed multivariate models to test the factors linked to the different outcomes, it is practically impossible to consider all the potential confounders in these formulations [36]. It should be remembered that the primary objective of this study was not focused on obesity as a comorbidity, but on the factors associated with remission and high activity in axSpA. Finally, our findings have not been characterized based on the different BMI categories, assuming obesity (BMI ≥ 30) as a categorical variable, which may ultimately be a somewhat crude approximation to the relationships between

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adiposity and inflammation in SpA. Among the strengths, it is worth highlighting the significant number of patients recruited from a unit specializing in this type of disease and subject to periodic quality audits.

5. Conclusions

In summary, both smoking and obesity are two factors associated with increased inflammatory activity in axSpA. However, since the obesity-activity relationship was only evident through the BASDAI in our study, and this is a highly subjective instrument, the factors governing the association between smoking, obesity, and increased axSpA activity could be very different. Therefore, the ASDAS seems a more reliable tool for daily clinical practice in this particular setting.

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