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Artículo original

Impacto de la obesidad en la actividad de la enfermedad en pacientes con espondiloartritis axial según el sexo

Gender-driven impact of obesity on disease activity in axial spondyloarthritis patients

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Palabras clave: obesidad; espondiloartritis axial; sexo.

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RESUMEN

Introducción: la obesidad desencadena inflamación y empeora las enfermedades reumáticas. Pocos estudios han abordado esta temática en la espondiloartritis axial (EspAax).

Objetivos: evaluar la composición corporal y su influencia en los parámetros inflamatorios de la EspAax según el sexo.

Materiales y métodos: se evaluó la masa corporal magra y la masa grasa mediante bioimpedancia en 60 pacientes con EspAax (30 hombres y 30 mujeres). Se utilizó BASDAI y ASDAS para evaluar la actividad de la enfermedad, y BASFI para evaluar la funcionalidad.

Resultados: de los 60 pacientes incluidos, 59 (98,3%) tenían masa grasa por encima de lo normal y masa magra por debajo de lo normal. Las mujeres presentaron menor masa magra que los hombres, mayor actividad de la enfermedad y peores puntuaciones funcionales. En los hombres, tanto la masa grasa como la magra, se correlacionaron con ASDAS (r 0,41; r -0,39, respectivamente) y BASFI (r 0,53 y r -0,60, respectivamente), mientras que no hubo correlaciones en las mujeres.

Conclusiones: las mujeres presentaron peor actividad de la enfermedad e índices funcionales que los varones. El aumento de la grasa corporal se correlacionó con la actividad de la enfermedad y los índices funcionales en los pacientes masculinos.

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Key words: *obesity; axial spondyloarthritis; sex.*

ABSTRACT

Introduction: obesity triggers inflammation and worsens rheumatic diseases. Few studies have addressed this issue in axial spondyloarthritis (axSpA).

Objectives: to evaluate the body composition and its influence on inflammatory parameters of axSpA according to sex.

Materials and methods: sixty axSpA patients (30 males and 30 females) had body composition, lean, and fat body mass assessed by bioimpedance. BASDAI and ASDAS were used to evaluate disease activity, and BASFI was used to evaluate physical function.

Results: of the 60 patients included, 59 (98.3%) had fat mass above the normal and lean mass under the normal range. Females had lower lean mass than males, higher disease activity, and worse functional scores. In males, both fat and lean mass correlate with ASDAS (r 0.41; r -0.39, respectively) and BASFI (r 0.53 and r -0.60), while there were no correlations in females.

Conclusions: females had worse disease activity and functional indexes than males. The increased body fat correlated with disease activity and functional indexes in male patients.

INTRODUCTION

Inflammatory control is a key factor in minimizing structural damage and atherosclerotic consequences in rheumatic diseases[1,2]. It also impacts the individual´s quality of life since uncontrolled inflammation has been associated with several patient-related outcomes (PROs), such as fatigue, pain, and disability[3].

Obesity is an important trigger of inflammation, and its role in aggravating the prognosis of rheumatic diseases is well-documented in rheumatoid arthritis, psoriatic arthritis, and systemic lupus erythematosus[4-6]. Proinflammatory cytokines, such as interleukin (IL)- 6 and tumoral necrosis factor (TNF)-α, as well as a large variety of adipokines such as leptin, resistin and visfatin which are mainly produced by the white adipose tissue, moderate the relationship between fat mass and inflammation[7,8]. Obesity has played a significant role in rheumatic disease control, as the prevalence of obesity in the general population is also increasing due to current dietary habits and sedentary behavior[8].

In patients with rheumatic diseases, the use of body mass index (BMI) as a measurement of obesity may be misleading[9]. These individuals may have excess adipose tissue while having normal or even low BMI; this measurement does not accurately reflect the proportion between fat and lean body mass. It is not uncommon that these individuals may suffer from obese cachexia, a term coined to highlight the imbalance between body weight and the proportion of fat mass that has been associated with chronic inflammation[10]. Consequently, obesity is better evaluated using instruments to measure body composition in these patients.

Axial spondylarthritis (axSpA) is a disease that affects young subjects, causing inflammatory back pain, peripheral arthritis, enthesitis, and uveitis. Previously considered to be a male-dominated disease, it is now known to affect females commonly[11]. However, the spectrum of the disease may differ between males and females, making the diagnosis difficult. Females may have different forms of disease presentation, affecting the peripheral joints more frequently, resulting in worse physical function and poorer quality of life than males[11].

Few studies have addressed the influence of body composition in controlling the inflammatory activity of SpA according to the patient's sex. Cheng et al.[2] showed the influence of obesity in the clinical parameters of 105 patients with SpA and found that 72.3% of their sample had a BMI ≥27 Kg/m^2 and that obesity was associated with inflammation and disease activity. Nevertheless, these authors did not evaluate males and females separately. Rusman et al.[12], addressing the differences in SpA expression according to sex, state that males have higher radiological damage and radiographic progression while females have higher BASDAI and lower quality

of life, but they did not address the influence of obesity on this context. Therefore, this study aimed to analyze a sample of Brazilian males and females with axSpA to evaluate whether obesity influences inflammatory activity based on the individual´s sex.

MATERIALS AND METHODS

This was a cross-sectional study with a sample of convenience that included all patients who came for regular consultation in a single Rheumatology Center from the Brazilian Public Health System during the period of one year, according to pre-established inclusion and exclusion criteria and the willingness to participate in the study. The patients were invited to participate according to their appointment sequence.

To be included, the participants must have axSpA[13], and be over the age of 18. Pregnant women, those with any other associated inflammatory disease, chronic infection or neoplastic disease, chronic obstructive pulmonary disease, such as emphysema, known eating disorders, disorders with malabsorption, severe cardiac failure (New York Heart Association classification ≥3)[14], glomerular filtration rate ≤20 mL/min and with implantable metallic devices that precluded the use of bioimpedance were excluded.

The local Research Ethics Committee approved this study under protocol number 5.096.190, and all included patients signed an informed consent.

Data collection

The clinical and epidemiological data were collected from the medical history. They included sex, age, ethnic background, age at disease onset, smoking, disease duration, presence of peripheral involvement, uveitis, HLA-B27, and used medication.

The measurement of disease activity was assessed through erythrocyte sedimentation rate (ESR), C reactive protein (CRP), Ankylosing Spondylitis Disease Activity Score (ASDAS), and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). Values considered for ASDAS were: <1.3 = inactive disease; between 1.3 and 2.0 =low disease activity; between 2.1 and 3.4= high disease activity, and >3.5= very high disease activity[15]. Values ≥4 for BASDAI were considered as active disease[13]. Functional status was accessed by the Bath Ankylosing Spondylitis Functional Index (BASFI), an instrument with 10 questions assessing the difficulty of daily tasks. The score ranges from 0-10, with higher scores corresponding to greater functional limitation[16].

The nutritional evaluation was assessed using anthropometric evaluation, including weight and height for body mass index (BMI) calculation and waist and hip circumference measurements for waist-to-hip ratio. Waist-to-hip ratio values ≤0.85 for females and ≤0.90 for males were considered normal17. Body composition was assessed through electrical impedance analysis using a Bodystat 1500® device that measures fat percentage (%), fat mass (kg), lean mass percentage (%), lean mass (kg), body water percentage (%), body water mass (L), basal metabolism rate (kcal), estimated caloric need (kcal), and impedance at 50 Hz corrected for patient's age and sex.

Statistical analysis

Categorical data were expressed in percentages; continuous variables with normal distribution were analyzed as mean, and standard deviation (SD), and median and interquartile range were expressed as Q1-Q3 (IQR) for non-parametric distribution. Data normality was assessed using the Shapiro-Wilk test.

Males and females were compared based on the number of times their fat mass was over the upper normal limit for their age and sex and the number of times their lean body mass was below the lower normal limit for their age and sex.

The Chi-squared test was used to compare nominal data, while the unpaired t-test and the Mann-Whitney U test were used for numerical data. The Pearson and Spearman tests were used accordingly to determine correlations between anthropometrical parameters and activity and functional indexes.

A multiple regression model was performed using ASDAS as the dependent variable, and the independent variables included were sex, age, presence of HLA B27, presence of extra-articular manifestations, peripheral arthritis, and increased fat mass.

The adopted significance was 5%. Tests were performed using GraphPad Prism software version 8.0.0 for Windows, San Diego, California USA, "www.graphpad.com".

RESULTS

The sample consisted of 60 axSpA patients: 30 males and 30 females. The main characteristics of the included patients are shown in Table 1. None of the included patients had a diagnosis of inflammatory bowel disease, and all were patients with radiographic axSpA.

Except for one female patient, all patients had a percentage of fat mass above the normal range and a percentage of lean mass below. Table 2 shows that females had higher inflammatory indexes and lean mass than males. No differences were observed in the patients' age, clinical profile, number of patients in each BMI category, or abnormal waist-to-hip ratio.

Table 3 shows the clinical characteristics according to the lean mass below the normal range and the fat mass above the limit for age and sex. No statically significant associations were found.

Table 4 shows the correlation analysis between the number of times that fat mass was above the upper limit and the number of times that lean mass was below the lower normal limit for inflammatory and functional parameters. Table 4 also shows the correlation between the waist-to-hip ratio and BMI. Both fat and lean mass correlate with ASDAS in males, while there was no correlation in females.

A linear regression model showed that only males (β=0.81; 95%CI=0.10 to 1,51; p=0.02) and peripheral arthritis (β=0.69; 95%CI=0.01 to 1.36, p=0.04) were associated with worst ASDAS, adjusting by age, presence of HLA B27, presence of extra-articular manifestations, and the increased fat mass.

Table 1: Main features of the studied sample.

Age (years), mean ± SD		49.4±12.0
Ethnic background, n(%)	Caucasians	50 (83.3%)
	Afro descendants	10 (16.6%)
Age at diagnosis (years), mean ± SD		38.9±10.8
Smokers (ex and current), n(%)		5 (8.3%)
Uveitis, n(%)		22 (33.3%)
Peripheral arthritis, n(%)		32 (53.3%)
Positive HLA - B27, n(%)*		32 (57.1%)
ESR (mm), median (IQR)		21.5 (5.2-41.0)
CRP– mg/dL, median (IQR)		2.7 (1.0-4.9)
ASDAS, mean ±SD		2.8±1.1
BASDAI, median (IQR)		3.5 (1.7-5.3)
BASFI, median (IQR)		3.0 (1.4-5.4)
Treatment, n (%)		
Non-steroidal anti-inflammatory drugs		20 (33.8%)
Methotrexate		10 (16.9%)
Sulfasalazine		14 (23.7%)
Anti-TNFα		37 (61.6%)
Anti-IL17		4 (6.7%)

**- data available in 56 patients;*
n= number; ESR= erythrocyte sedimentation rate; CRP= C reactive protein; SD= standard deviation; IQR= interquartile range; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI= Bath Ankylosing Spondylitis Functional Index; ASDAS-Ankylosing Spondylitis Disease Activity Score.

Table 2: Comparison of age, clinical profile, anthropometric, inflammatory activity and functional parameters in males and females with ankylosing spondylitis.

		Males	Females	P value
Age (years), median (IQR)		50.5 (43.7-58.2)	49.0 (44.0-57.2)	0.7107
Caucasian ethnic, n(%)		25 (83.3%)	25 (83.3%)	1.000
Uveitis, n(%)		8 (26.6%)	12 (40%)	0.2733
Peripheral arthritis, n(%)		15 (50%)	17 (56.6%)	0.6048
Skin manifestations, n(%)		4 (13.3%)	2 (6.6%)	0.6707
ESR (mm), median (IQR)		10.0 (5.0-35.0)	28.0 (10.5-67.5)	0.0096
CRP (mg/dL), median (IQR)		1.7 (0.9-3.2)	4.0 (1.6-10.6)	0.0183
ASDAS, mean ±SD		2.3 ± 1.0	3.2 ± 1.0	0.0021
BASDAI, mean ±SD		2.9 ± 2.0	4.3 ± 2.4	0.0173
BASFI, median (IQR)		2.4 (0.8-3.2)	4.3 (1.8-6.3)	0.0500
BMI, n(%)				
	Normal	9 (30%)	8 (26.6%)	0.8731
	overweight	12 (40%)	14 (46.6%)	
	Obese	9 (30%)	8 (26.6%)	
Waist-to-hip ratio (normal), n(%)		10 (33.3%)	13 (43.3%)	0.4257
Fat mass (*), median (IQR)		1.71 (1.52-1.83)	1.60 (1.49-1.76)	0.1960
Lean mass (**), median (IQR)		0.81 (0.79-0.86)	0.74 (0.68-0.79)	<0.0001

**Number of times that fat mass was above the normal superior threshold.*
***Number of times that the lean mass was under the normal inferior threshold for age and sex.*
ESR= erythrocyte sedimentation rate; CRP= C reactive protein, BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI= Bath Ankylosing Spondylitis Functional Index; ASDAS- Ankylosing Spondylitis Disease Activity Score; BMI= body mass index; n= number; IQR= interquartile range; SD= standard deviation.

Table 3: Fat and lean mass according to clinical profile in males and females with axial spondyloarthritis.

	MALES			FEMALES		
	With the variable	Without the variable	P	With the variable	Without the variable	P
FAT MASS (*)						
Caucasian ethnic background	1.70±0.33	1.62±0.12	0.5834	1.64±0.15	1.62±0.26	0.7532
Uveitis	1.85±0.44	1.63±0.23	0.0842	1.65±0.18	1.62±0.16	0.4103
Peripheral arthritis	1.77±0.37	1.60±0.21	0.1406	1.58±0.44	1.58±0.14	0.2287
Psoriasis	1.80±0.21	1.67±0.32	0.4348			
HLA B27	1.67±0.22	1.63±0.26	0.7828	1.63±0.16	1.60±0.13	0.7106
LEAN MASS (**)						
Caucasian ethnic background	0.81±0.08	0.84±0.03	0.3295	0.70±0.16	0.74±0.10	0.4429
Uveitis	0.78±0.11	0.83±0.06	0.1204	0.62±0.28	0.73±0.08	0.5520
Peripheral arthritis	0.78±0.10	0.84±0.05	0.0812	0.67±0.19	0.74±0.08	0.2328
Psoriasis	0.79±0.05	0.82±0.08	0.5479			
HLA B27	0.82±0.06	0.84±0.06	0.5886	0.72±0.07	0.69±0.22	0.9755

** Fat mass above the normal superior threshold*
*** Lean mass under the normal inferior threshold for age and sex. Skin manifestations not studied in females due to small number (n=2).*

Table 4: Correlation studies of fat and lean mass with axial spondyloarthritis activity and functional indexes.

	R	95%CI	P
MALES			
FAT MASS			
BASDAI	0.31	-0.05 to 0.61	0.0866
ASDAS	0.41	0.03 to 0.68	0.0277
ESR	0.21	-0.18 to 0.56	0.2759
CRP	0.25	-0.13 to 0.58	0.1867
BASFI	0.53	0.2 to 0.75	0.0025
LEAN MASS			
BASDAI	-0.45	-0.70 to -0.11	0.0373
ASDAS	-0.39	-0.67 to – 0.02	0.0348
ESR	-0.23	-0.57 to 0.16	0.2344
CRP	0.08	-0.29 to 0.44	0.2153
BASFI	-0.60	-0.79 to -0.30	0.0004
WAIST-TO-HIP RATIO			
BASDAI	0.20	-0.17 to 0.52	0.2930
ASDAS	0.08	-0.30 to 0.44	0.6556
ESR	0.31	-0.08 to 0.62	0.1064
CRP	0.19	-0.20 to 0.53	0.3163
BASFI	0.48	0.13-0.72	0.0072
BMI			
BASDAI	0.42	0.08 to 0.68	0.0108
ASDAS	0.58	0.27 to 0.73	<0.0001
ESR	0.03	-0.35 to 0.41	0.8605
CRP	0.42	0.04 to 0.69	0.0247
BASFI	0.61	0.31 to 0.80	0.0003
FEMALES			
FAT MASS			
BASDAI	-0.05	-0.41 to 0.32	0.7820
ASDAS	-0.03	-0.40 to 0.34	0.8640
ESR	-0.19	-0.53 to 0.19	0.3014
CRP	0.13	-0.25 to 0.48	0.4754
BASFI	0.18	-0.20 to 0.51	0.3403
LEAN MASS spearman			
BASDAI	-0.02	-0.39 to 0.34	0.9006
ASDAS	-0.21	-0.54 to 0.17	0.2710
ESR	-0.03	-0.40 to o.34	0.8699
CRP	-0.26	-0.58 to 0.12	0.1668
BASFI	-0.27	-0.58 to 0.10	0.1342
WAIST-TO-HIP RATIO			
BASDAI	-0.12	-0.48 to 0.26	0.5053
ASDAS	0.12	-0.26 to 0.48	0.5141
ESR	0.25	-0.14 to -0.57	0.1962
CRP	0.04	-0.34 to 0.42	0.8162
BASFI	0.23	-0.15 to 0.56	0.2136
BMI			
BASDAI	-0.08	-0.43 to 0.28	0.6592
ASDAS	0.05	-0.31 to 0.41	0.7695
ESR	-0.22	-0.55 to 0.16	0.2134
CRP	0.18	-0.20 to 0.52	0.3465
BASFI	-0.13	-0.47 to 0.23	0.4786

ESR= erythrocyte sedimentation rate; CRP= C reactive protein; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI= Bath Ankylosing Spondylitis Functional Index; ASDAS- Ankylosing Spondylitis Disease Activity Score, BMI= body mass index.

DISCUSSION

This study showed that females had worse inflammatory and functional parameters than males. In addition, from an anthropometric standpoint, females had lower lean mass than males, whereas BMI distribution, waist-to-hip ratio, and number of times that fat mass was increased were equivalent between males and females. Nevertheless, only males had a moderated correlation between increased fat mass and inflammatory and functional parameters. The multiple regression model showed that fat was not independently linked to disease activity while sex was, suggesting that the influence of obesity in disease activity may be linked to the gender.

Differences between males and females with axSpA have been previously reported. Regarding clinical profile, females were shown to have more peripheral involvement and worse patient-related outcomes than males[18-22]. Males were more likely to have HLA B27 positive results[18,19]. Inflammatory parameters have also been found to differ by sex. The BASDAI has been reported to be higher in females than males in several other studies[11,20,22-25], and it has also been reported in this study. In contrast, the ASDAS comparison between genders has shown contradictory results. Van der Horst-Bruinsma et al.[26] and Webers et al.[27] did not find sex differences in the ASDAS index. However, Benavent et al.[24] reported higher scores among females with axSpA, which has also been found in the present study.

A key finding in the present study was the correlation between the increase in fat mass and inflammatory and functional parameters in males but not in females, indicating that the influence of obesity on axSpA may differ according to gender. A study about body composition in the Netherlands by Ibáñez-Vodnizza et al.[28], with 70 ankylosing spondylitis (AS), found that high disease activity was associated with a lower percentage of body fat in males and a higher percentage of body fat in females. In contrast, the present study showed that high-fat mass was associated with a higher inflammatory response in males. Although there is no clear explanation for the discrepancy between our findings and those of Ibáñez Vodnizza et al., it is worth acknowledging that ethnicity may have influenced the results. Rush et al.[29], studying fat distribution in females from five ethnic groups, found that different ethnic groups had differences in body fat distribution, and other studies found that for a given amount of subcutaneous and visceral fat, the systemic repercussions may vary according to the patient's ethnic background[29,30]. Ethnicity has also been shown to influence the cut-off points used to determine waist circumference[29].

The variability of fat percentage in disease activity in males and females suggests that this disease may follow pathophysiologic pathways that differ according to gender. One study was on the disease's cytokine profile, and males had elevated levels of IL-17A and Th17 cells, key factors in the inflammatory Th17 axis, while females did not[31]. Another study showed that males had higher levels of TNF alpha and IL-18[12], whereas females had higher levels of IL-6[23]. A second relevant difference is in the genetic background: genes such as ANKH, which encodes a progressive ankylosing protein involved in the structural damage of axSpA, have different loci association according to sex[12]; the same with TNAP (tissue-nonspecific alkaline phosphatase) haplotype that has been found in males but not in females with AS[12]. According to Gracey et al.[31], 650 genes have exhibited different expressions in males and females. Finally, sexual hormones may also play a role. Estrogens have been found to decrease inflammatory activity, but inconsistent findings have been reported in axSpA[12,32-34].

This study has several limitations that need to be acknowledged, such as sample size, the cross-sectional design, and the use of bioimpedance for the study of body composition. The use of dual-energy X-ray absorptiometry (DEXA) is considered to be more accurate. Furthermore, the sample had low disease activity, which may have precluded certain findings. Another point that needs to be addressed is that BASDAI and ASDAS, although widely accepted to evaluate disease activity, include subjective parameters that can be influenced by comorbidities such as fibromyalgia, which is more common in females and could have had some impact on the results. Also, evaluating other parameters such as physical activity and BASMI (Bath ankylosing spondylitis metrology index) would be enlightening. Nevertheless, this research emphasizes the need to consider patients' gender when studying axSpA patients.

CONCLUSIONS

In this sample of Brazilian patients with axSpA, females had worse disease activity and functional indexes than males. No differences were found in the proportion of increased fat, BMI, and waist-to-hip ratio, but lean body mass was lower in females. Moreover, in male axSpA patients, the proportion of increased body fat correlated with disease activity and functional indexes.

This study is a starting point for further research on the differences in the clinical expression of SpA according to sex, including the influence of obesity on the inflammatory parameters of this disease.

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