ORIGINAL ARTICLES

Sex differences in axial spondyloarthritis: data from a Portuguese spondyloarthritis cohort

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ABSTRACT

Background: Axial spondyloarthritis (axSpA), particularly ankylosing spondylitis was historically considered a male's disease and has been under-recognized in women.
Emerging evidence reveals sex differences in pathophysiology, disease presentation and therapeutic efficacy.
Objective: To identify differences between sexes in a Portuguese cohort of patients with axSpA regarding clinical manifestations, disease activity, functional capacity, patient related outcomes and presence of sacroiliitis on x-ray or magnetic resonance imaging.
Methods: Patients with ≥18 years fulfilling the ASAS- Assessment of Spondyloarthritis International Society classification criteria for axSpA registered in the electronic Rheumatic Diseases Portuguese Register (Reuma.pt) were included in this multicentric cross-sectional study. Sociodemographic data, clinical features and imaging were collected from the first record in Reuma.pt. These variables were compared between sexes using Mann-Whitney test and Chi-Square test. Variables with a significant association with variable sex were considered in the multiple variable analysis to adjust the sex effect on the outcome variables. Statistical analysis was performed with R version 4.0.2 and $p<0.05$ was considered statistically significant.
Results: A total of 1995 patients were included, 1114 (55.9%) men and 881 (44.1%) women. Men had an earlier disease onset (25.1 vs 28.4, $p<0.001$), were younger at diagnosis (26.9 vs 30.4, $p<0.001$) and were more frequently smokers (32.1% vs 15.7%, $p<0.001$). Comparing to women, men had worse Bath Ankylosing Spondylitis Metrological Index scores (4.0 vs 3.4, $p<0.001$), higher levels of C-Reactive Protein (10.5 vs 6.9 mg/L, $p<0.001$) and were more often Human Leukocyte Antigen-B27 positive (67.8% vs 54%, $p<0.001$).
In contrast, women more frequently had inflammatory bowel disease (8.8% vs 4.9%, $p=0.004$), higher levels of erythrocyte sedimentation rate (25.0 vs 21.0mm/h, $p=0.003$) and worse patient-related outcomes- Bath Ankylosing Spondylitis Disease Activity Index (5.7 vs 4.5, $p<0.001$), Patient Global Assessment (60.0 vs 50.0, $p<0.001$) and fatigue (6.2 vs 5.0, $p<0.001$).
Discussion: In this large multicentric study from a Portuguese axSpA cohort, we confirmed sex differences in patients with axSpA. This work brings awareness to these differences, resulting in less underdiagnosis and misdiagnosis, optimizing treatment strategies, and improving outcomes in axSpA.

Keywords: Axial spondyloarthritis; Sex; Extra-articular manifestations; Disease activity; Imaging.

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INTRODUCTION

Spondyloarthritis (SpA) is a group of chronic inflammatory rheumatic diseases that can affect the axial skeleton and the most common symptom is chronic inflammatory lower back pain. Other musculoskeletal manifestations included arthritis, dactylitis and enthesitis. Extra-articular manifestations can also occur, namely psoriasis, inflammatory bowel disease and uveitis[1].

Axial spondyloarthritis (axSpA) is a term used to classify patients with predominantly axial involvement and encompasses ankylosis spondylitis (AS) with radiographic sacroiliitis and non-radiographic axSpA (nr-axSpA)[2].

For a long period of time, axSpA, in particular AS, was considered a disease that occurred mostly in men. Currently, it is estimated that the ratio male to female is ~ 2-3:1[3]. The under-recognition of this disease in women can lead to a delay in diagnosis[4] and therefore retard the implementation of treatment strategies and contributing to increased disease burden in female axSpA patients. The reasons for this difference remain unclear.

These sex differences may be due to different immunological, hormonal, and genetic determinants[5].

Men with AS, but not women, have elevated levels of Tumor Necrosis Factor alfa (TNFα) and interleukin (IL) -17A compared to controls[6]. IL-17A acts synergistically with TNF to affect inflammatory pathways and these differences between sexes may influence the axial radiographic changes[7].

In addition, in male patients with AS and syndesmophytes, IL-18 levels are elevated, while women had significantly higher IL-6[8].

A distinct locus of the ANK gene was identified in male patients with AS. This gene encodes an ANKH protein that is associated with damage observed in axSpA patients[9].

Another relevant difference was found in tissue-nonspecific alkaline phosphatase (TNAP) haplotype, which is associated with AS in men but not in women[10].

Hormonal differences between sexes might also play a role in SpA manifestations. Estrogen inhibits TNFα production, potentially affecting inflammatory pathways, although contradicting results were reported and further investigation is needed[11].

Regarding clinical features, men with AS have more severe radiographic damage, more inflammation[12–14] and are more often HLA-B27 positives[15,16]. On the other hand, some authors reported that women with AS had more often peripheral involvement[12,15,17–20] and worse patient related outcomes (PROs)[14,15,18,19,21].

The aim of this study was to determine if there are differences between sexes in a Portuguese cohort of patients with axSpA regarding clinical data (disease manifestation, disease activity, functional capacity, PROs and imaging findings).

METHODS

Study population

Eligible patients were over 18 years and fulfilled the ASAS (Assessment of Spondyloarthritis International Society) classification criteria for axSpA, registered in the electronic national database - Rheumatic Diseases Portuguese Register (*Reuma.pt*).

Patients with axSpA, whose disease started between 1980-2020, were included. All patients signed informed consent.

Study design and data collection

This was a multicentric cross-sectional study. All patient data were anonymised and collected in accordance with national legal and regulatory requirements.

The following data were collected from the first record in *Reuma.pt:* sociodemographic - age, sex, Body Mass Index (BMI, calculated using self-reported weight and height), smoking habits (smoker, no smoker, ex-smoker), marital status, educational level, clinical data - duration of symptoms until diagnosis (diagnostic delay), presence of axial (inflammatory low back pain), peripheral (peripheral arthritis) and extra-articular manifestations [(enthesitis, uveitis, dactylitis, psoriasis, inflammatory bowel disease (IBD)], family history of SpA; disease activity - Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis Disease Activity Score- C-Reactive Protein (ASDAS-CRP); functional capacity - Bath Ankylosing Spondylitis Functional Index (BASFI), mobility- Bath Ankylosing Spondylitis Metrological Index (BASMI); Patient Global Assessment (PGA) and Physician Global Assessment (PhGA); fatigue, assessed by the first question of BASDAI. Laboratory data included acute phase reactants - C-Reactive Protein (CRP) (mg/L), Erythrocyte Sedimentation Rate (ESR) (mm/h) and Human Leukocyte Antigen-B27 (HLA-B27). Imaging findings such as sacroiliitis on radiography, defined by modified New York criteria (mNY) or/and magnetic resonance imaging (MRI), according to ASAS criteria, were also collected.

Statistical analysis

Descriptive analysis of sociodemographic, clinical, disease activity, laboratory and imaging was performed using absolute and relative frequencies for categorical variables and median and interquartile ranges for numerical variables.

The groups were compared using Mann-Whitney test for continuous variables and Chi-Square test for

categorical variables.

The variables with significant association with the variable sex were considered in the multiple variable analysis to adjust the sex effect on the outcome variables.

We performed univariate analysis, followed by multivariable analysis, using linear regression and logistic regression models according to the outcome variable type.

For all presented models, the observations with missing variables included in the analysis were removed. Only complete cases were considered.

The variance inflation factor (VIF) and correlation measures were used to assess multicollinearity. An analysis of sensitivity to exclude outliers was made on the estimates of the coefficients and significance of the models' independent variables.

Statistical analysis was performed with R version 4.0.2 and $p<0.05$ was considered statistically significant.

RESULTS

In total, 1995 patients were included, 1114 (55.9%) men and 881 (44.1%) women. The patients' sociodemographic and clinical characteristics are presented in Table I.

The median age at disease onset (25.1 vs 28.4, p<0.001) and the median age at diagnosis (26.9 vs 30.4, p<0.001) were lower for men than women. However, no significant difference was found in duration of symptoms until diagnosis (diagnostic delay) between sexes.

Two hundred and fifty (32.1%) men were smokers in comparison with ninety-three women (15.7%) (p<0.001).

With regard to axSpA manifestations, only inflammatory bowel disease was more prevalent in women than in men (8.8% vs 4.9%, p=0.004).

Spinal mobility, measured by BASMI, scored worse in men than women (4.0 vs 3.4, p<0.001). There were no differences between sexes regarding physical function (BASFI).

On the opposite, worse PROs - BASDAI (5.7 vs 4.5, p<0.001), PGA (60.0 vs 50.0, p<0.001) and fatigue (6.2 vs 5.0, p<0.001) were reported by women than men.

Higher CRP levels (10.5 vs 6.9 mg/L, p<0.001) were seen in men compared with women. In contrast, women had higher ESR than men (25.0 vs 21.0 mm/h, p=0.003).

HLA-B27 positivity was more frequent in men (67.8% vs 54.0%, p<0.001).

Radiographic or/and MRI sacroiliitis, was more common in men than women (95.5% vs 91.7%, p=0.004).

In univariable analysis, male sex was associated with higher score of BASMI (β 0.74 [95% CI 0.50, 0.98; p<0.001]) and presence of sacroiliitis on radiography or/and MRI (OR=1.92 [95% CI 1.23, 3.02; p= 0.004). On the other hand, male sex was associated with lower scores of BASDAI (β -0.90 [95% CI -1.13, -0.66; p<0.001]), PGA (β -5.86 [95% CI -8.78,-2.95; p<0.001]) and fatigue (β -1.38 [95% CI -1.65, 1.12; p< 0.001).

In multivariable analysis (Table II), BASDAI was positively associated with ESR (β 0.02 [95% CI 0.02, 0.03; p= <0.001]) and negatively associated with male sex (β -0.96 [95% CI -1.29, -0.63; p= <0.001]), HLA-B27 (β -0.50 [95% CI -0.82, -0.19; p= 0.002]) and IBD (β -0.70 [95% CI-1.27, -0.12; p= 0.018]).

Higher BASMI score was associated with male sex (β 0.65 [95% CI 0.27, 1.03; p= 0.001]), smoking (β 0.86 [95% CI 0.43,1.30; p< 0.001]), older age at diagnosis (β 0.02 [95% CI 0.01, 0.04; p=0.002]) and more elevated ESR levels (β 0.01 [95% CI $5.15x10^{-3}$, 0.02; p< 0.001]).

PGA score was positively associated with ESR levels (β 0.31 [95% CI 0.24, 0.39; p=<0.001)] and negatively associated with HLA-B27 (β -7.96 [95% CI -11.86, -4.06; p=<0.001)] and male sex (β -5.77 [95% CI -9.85, -1.69; p=0.006]).

Higher fatigue score was associated with more elevated levels of ESR (β 0.02 [95% CI 0.02, 0.03; p= <0.001], presence of IBD (β -0.80 [95% CI -1.50, -0.10 ; p= 0.024]) and female sex (β -1.32 [95% CI -1.71, -0.92; p<0.001]).

No statistically significant association was found in multivariate analysis between sacroiliitis on radiograph or/and MRI and the independent variables tested.

DISCUSSION

In this large multicentric study from a Portuguese axSpA cohort, we confirmed sex differences in these patients. Some of our results were in line with the available data, but we also found conflicting results.

As previously demonstrated[22], in this cohort men with axSpA had an earlier onset of disease and younger age at diagnosis. However, we did not confirm a longer diagnostic delay in women, as suggested by a meta-analysis covering 42 studies and 23889 patients[4]. We hypothesize that, since this was a relatively young cohort, the wide availability of imaging methods, namely MRI, could explain a more prompt diagnosis.

In contrast, a longer delay in women found in other articles could be explained by less severe disease or slower progression of radiographic damage in this sex and the differential diagnosis with other pathologies such as fibromyalgia, mechanical back pain or widespread pain[23–25].

In line with previous studies, we found that smoking habits were more frequent in men than women[26,27]. Moreover, it was well-known the association between smoking and global disease activity, measured by

Table I. Socio-demographic, clinical data and imaging between sexes

	Total (n=1995)	Women (n=881)	Men (n=1114)	p value	Missing data (n)
Current age, years [median (IQR)]	50.0 (19.0)	49.0 (18.0)	50.0 (20.0)	0.500	0
Age at onset, years [median (IQR)]	26.5 (14.4)	28.4 (14.9)	25.1 (13.7)	<0.001	541
Age at diagnosis, years [median (IQR)]	28.5 (16.1)	30.4 (15.4)	26.9 (15.6)	<0.001	538
Disease duration, years [median (IQR)]	18 (16)	16 (14)	19 (17)	<0.001	538
Delay in diagnosis, years [median (IQR)]	0 (0.1)	0 (0.0)	0 (0.5)	0.311	533
BMI [median (IQR)]	25.6 (7.9)	25.4 (6.3)	25.6 (5.5)	0.838	1032
Smoking n (%)	343 (25.0)	93 (15.7)	250 (32.1)	<0.001	623
Educational level n (%)				0.824	969
Elementary School	346 (33.7)	139 (32.7)	207 (34.4)		
Middle School	162 (15.8)	63 (14.8)	99 (16.5)		
High School	251 (24.5)	111 (26.1)	140 (23.3)		
Higher Education	258 (25.1)	108 (25.4)	150 (25.0)		
Illiteracy	9 (0.9)	4 (0.9)	5 (0.8)		
Marital Status n (%)				0.209	958
Single	259 (25.0)	107 (22.2)	152 (27.4)		
Married	709 (68.4)	341 (70.6)	368 (66.4)		
Divorced	38 (3.7)	18 (3.7)	20 (3.6)		
Other	14 (1.3)	6 (1.2)	8 (1.4)		
Widowed	17 (1.6)	11 (2.3)	6 (1.1)		
Peripheral arthritis n (%)	476 (33.2)	190 (32.6)	286 (33.5)	0.727	560
Enthesitis n (%)	320 (22.3%)	135 (23.2%)	185 (21.7%)	0.500	560
Uveitis n (%)	295 (20.6)	123 (21.1)	172 (20.2)	0.655	560
Dactylitis n(%)	60 (4.2)	23 (4.0)	37 (4.3)	0.720	560
Psoriasis n (%)	49 (3.4)	19 (3.3)	30 (3.5)	0.796	560
IBD n (%)	93 (6.5)	51 (8.8)	42 (4.9)	0.004	560
Low back pain n (%)	1250 (87.1)	501 (86.1)	749 (87.8)	0.338	560
Family history of spondyloarthritis n (%)	187 (13.0)	74 (12.7)	113 (13.2)	0.769	560
ASDAS-CRP 0-10 [median (IQR)]	3.3 (1.6)	3.3 (1.4)	3.2 (1.8)	0.056	812
BASDAI 0-10 [median (IQR)]	5.0 (3.7)	5.7 (3.2)	4.5 (3.9)	<0.001	366
BASFI 0-10 [median (IQR)]	4.7 (4.5)	4.8 (4.4)	4.6 (4.4)	0.101	696
BASMI 0-10 [median (IQR)]	3.6 (2.6)	3.4 (1.6)	4.0 (3.4)	<0.001	1142
PGA 0-100 [median (IQR)]	55.0 (46.0)	60.0 (47.5)	50.0 (49.7)	<0.001	423
PhGA 0-100 [median (IQR)]	40.0 (45.0)	40.0 (40.0)	40.0 (50.0)	0.405	1163
Fatigue 0-10 [median (IQR)]	5.4 (4.4)	6.2 (3.9)	5.0 (4.8)	<0.001	352
CRP (mg/L) [median (IQR)]	8.0 (18.3)	6.9 (13.3)	10.5 (23.3)	<0.001	645
ESR (mm/h) [median (IQR)]	23.0 (37.0)	25.0 (34.0)	21.0 (40.0)	0.003	640
HLA-B27 n (%)	892 (62.2)	314 (54.0)	578 (67.8)	<0.001	560
Sacroiliitis on radiography or/and MRI n (%)	1284 (94.0)	498 (91.7)	786 (95.5)	0.004	629

IQR: Interquartile Ranges; n: number; BMI: Body Mass Index; IBD: inflammatory bowel disease; ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score-C-Reactive Protein; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrological Index; PGA: Patient Global Assessment; CRP: C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate; ; HLA-B27: Human Leukocyte Antigen-B27; MRI: Magnetic Resonance Imaging

Table II. Multivariable analysis to adjust the sex effect on the outcome variables

	BASDAI		BASMI		PGA		Fatigue		Sacroiliitis on radiograph or/and MRI	
	β	p	β	p	β	p	β	p	OR	p
Male sex	-0.96	<0.001	0.65	0.001	-5.77	0.006	-1.32	<0.001	1.88	0.075
Age at diagnosis	0.00	0.629	0.02	0.002	-0.06	0.475	0.01	0.438	1.00	0.978
HLA-B27	-0.50	0.002	-0.25	0.164	-7.96	<0.001	-0.36	0.064	0.84	0.628
CRP	0.00	0.164	0.00	0.214	0.02	0.589	0.00	0.457	1.00	0.837
Smoker	0.06	0.739	0.86	<0.001	4.09	0.080	0.25	0.261	1.40	0.425
Ex-smoker	0.17	0.420	0.63	0.010	3.94	0.133	0.30	0.232	2.47	0.151
IBD	-0.70	0.018	-0.33	0.289	-1.95	0.595	-0.80	0.024	0.95	0.932
ESR	0.02	<0.001	0.01	<0.001	0.31	<0.001	0.02	<0.001	1.01	0.400

OR: Odds ratio; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASMI: Bath Ankylosing Spondylitis Metrological Index; PGA: Patient Global Assessment; HLA-B27: Human Leukocyte Antigen-B27; CRP: C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate; IBD: Inflammatory Bowel Disease; MRI: Magnetic Resonance Imaging

BASDAI[28]. There is also good evidence revealing that cigarette smoking[29] and smoking intensity[30] was associated with spinal radiographic progression in axSpA.

The predominant prevalence of some extra-manifestations, according to sex, remains uncertain. Our study demonstrated a higher prevalence of IBD in female sex and this is an extra-articular manifestation whose frequency is unanimously cited as having a sex prevalence[15,17,31]. The data regarding other extra-articular manifestations varies widely, however previous studies suggested that psoriasis[17,32], dactylitis[15,18,19] and enthesitis[12,15,18–20,33] were more frequent in women and other evidence suggested that the occurrence of acute anterior uveitis was more frequent in men[13,18].

Concerning disease burden, PROs tend to be worse in women[34], especially the BASDAI items of total back pain, duration of morning stiffness and fatigue[12,13,14–16,18–21,35,36,37]. The exception is BASFI, where sex dominance was not reported[15] or high scores were found in women[34]. Although comorbidities were not assessed, the well-known higher prevalence of generalized pain syndromes in women might account for the differences found.

Still regarding disease activity, CRP was higher in men, as reported in other studies[13,15,20,33]; on the other hand, ESR was significantly higher in women. The actual evidence regarding sex differences was inconclusive[5,34]. In our point of view, the higher levels of ESR in women found, in our study, were not relevant and can be justified with the already different cut-off levels for normal ESR levels by sex.

Since PROs (BASDAI and PGA) were higher in women but CRP was lower in this sex, ASDAS-CRP was similar between sexes, as previously reported in the literature[13,14].

The more frequent presence of HLA-B27, which has been reported in some studies[15,16], along with a higher percentage of smokers and increased CRP in male, might reflect the main reasons why we found a higher frequency of imaging findings in men at baseline in univariate analysis. This finding is not surprising, since other cohorts also described the higher frequency of MRI and radiographic positivity of the sacroiliac joints.

Thus, in line with a previous report that described worse mobility in men with axSpA[23], BASMI score was unsurprisingly more elevated in males[15,35].

Our study has some limitations. First, this is a cross-sectional study, so we didn't evaluate imaging progression; second, the results can be associated with information bias and be influenced by an unbalanced sample and *missing data*. Regarding missing data, in the final model, CRP was the variable that presented more missing data (n=645), therefore the complete cases used in multiple regression analysis are n=1350. Third, regarding the diagnostic delay, the year of diagnosis and onset of symptoms was the same in many of our patients, resulting in the absence of diagnostic delay. Data registration bias contributes to these results, therefore, the reported differences between sexes are possibly biased. We believe that real differences present a higher effect size. Third, we didn't exclude patients with some comorbidities such as fibromyalgia, which can affect some disease activity scores. Fourth, we didn't collect data about treatment. In further research, we can evaluate differences between sexes, concerning the effectiveness of the treatment (eg. tumor necrosis factor

inhibitors).

CONCLUSION

The paradigm has changed and axSpA is no longer seen as a male disease.

Physicians must be aware of these differences because this can prevent underdiagnosis and misdiagnosis of axSpA in women and therefore allow optimization of treatment strategies and improve outcomes of axSpA.

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