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Sex differences in cardiovascular and disease-related features in axial spondyloarthritis. A multicenter study of 912 patients

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ABSTRACT

Objectives: To determine the potential impact of sex-specific disease-related characteristics on cardiovascular (CV) disease in axial spondyloarthritis (axSpA).
Methods: Cross-sectional study of the Spanish AtheSpAin cohort to study CV disease in axSpA. Data on carotid ultrasound and CV disease and disease-related features were collected.
Results: 611 men and 301 women were recruited. Classic CV risk factors were significantly less prevalent in women, who also showed a lower frequency of carotid plaques ($p = 0.001$), lower carotid intima-media thickness (IMT) values ($p<0.001$) and CV events ($p = 0.008$). However, after adjustment for classic CV risk factors, only the differences with respect to carotid IMT remained statistically significant. Women showed higher ESR at diagnosis ($p = 0.038$), and more active disease (ASDAS, $p = 0.012$, and BASDAI, $p<0.001$). They had shorter disease duration ($p<0.001$), lower prevalence of psoriasis ($p = 0.008$), less structural damage (mSASSS, $p<0.001$), and less mobility limitation (BASMI, $p = 0.033$). To establish whether these findings could lead to sex differences in

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CV disease burden, we compared the prevalence of carotid plaques in men and women with the same level of CV risk stratified according to the Systematic Coronary Risk Evaluation (SCORE). Men included in the low-moderate CV risk SCORE category had more carotid plaques ($p = 0.050$), along with longer disease duration ($p = 0.004$), higher mSASSS ($p = 0.001$) and psoriasis ($p = 0.023$). In contrast, in the high-very high-risk SCORE category, carotid plaques were observed more frequently in women ($p = 0.028$), who were characterized as having worse BASFI ($p = 0.011$), BASDAI ($p<0.001$) and ASDAS ($p = 0.027$).

Conclusion: Disease-related features may influence the expression of atherosclerosis in patients with axSpA. This may be especially applicable to women at high CV risk, characterized by greater disease severity and more severe subclinical atherosclerosis than men, suggesting a stronger interaction between disease activity and atherosclerosis in women with axSpA.

Introduction

Axial spondyloarthritis (axSpA) is a chronic inflammatory rheumatic disorder characterized by chronic back pain with an onset before the age of 45 years. This term, proposed by the Assessment of SpondyloArthritis International Society (ASAS) in 2009, encompasses both patients with radiographic evidence of sacroiliitis (r-axSpA), also known as ankylosing spondylitis (AS), and others without it, who are classified as non-radiographic axSpA (nr-axSpA) [1].

In contrast to the men predominance characterizing classic AS, men and women are equally represented in nr-axSpA[2]. In parallel with the decline of the men: women ratio observed in axSpA in recent years [3], an increasing interest in elucidating sex-related differences in disease manifestations has been noticed. Most studies coincide in describing a different phenotype of the disease depending on the sex [3]. Women are characterized by a higher disease activity measured by BASDAI, more frequent peripheral arthritis and enthesitis, and a closer association with extraarticular manifestations such as psoriasis (Ps) and inflammatory bowel disease (IBD). In contrast, men exhibit higher serum levels of C reactive protein (CRP) and more severe structural damage. Nevertheless, it is less clear whether other features, such as the functional limitation according to BASFI or the coexistence of anterior uveitis, show differences between men and women axSpA patients, and information on the most critical comorbidities are scarce or even absent [3].

Although CV disease is increased in axSpA and remains the leading cause of morbidity and mortality among these patients [4,5]studies assessing sex differences in this regard are lacking. A study from a British database including 3809 patients with newly diagnosed AS reported a non-significant trend toward an increased risk of developing ischemic heart disease only in women [6]. However, this finding has not been confirmed in subsequent studies, and the authors did not find any explanation for this difference. In contrast, Haroon et al. reported a significantly increased hazard ratio for vascular mortality in men but not women [1.46 (95% CI 1.13 to 1.87) versus 1.24 (0.92 to 1.67)] in an AS cohort from Ontario [7]. This is an intriguing controversy to elucidate, considering that some of the sex-related differentiating characteristics previously mentioned have also been associated with subclinical atherosclerosis [8,9], and their potential influence on the CV risk of both sexes is unknown. Besides, sex-specific differences also exist regarding traditional CV risk factors between men and women in the general population, with men showing a higher prevalence of hypertension, dyslipidemia, or diabetes [10]. These classic CV risk factors seem to have a close relationship with inflammation in chronic inflammatory disorders (8), and it is unknown whether sex peculiarities in this interaction may exist, thus leading to differences in the atherogenic burden of men and women patients with axSpA.

The AtheSpAin study encompasses a large Spanish multicenter cohort designed to analyze atherosclerotic disease in axSpA. The present study aimed to better characterize the CV risk of men and women with axSpA and to determine the impact that sex-based differences in disease manifestations may have on atherosclerosis of both sexes.

Materials and methods

Patients

This is a cross-sectional analysis of the AtheSpAin cohort. For this purpose, consecutive patients older than 18 years who met the radiographic definitions of axSpA (r-axSpA) and nr-axSpA according to the ASAS criteria [1]were recruited for six years (2013–2019) in 12 different Spanish hospitals.

We reviewed information on disease duration, HLA-B27 status, hip involvement, synovitis, enthesitis, and therapy from the disease diagnosis. It was also the case for information on extra-articular manifestations, including psoriasis, inflammatory bowel disease, and acute anterior uveitis, as well as data on C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) levels at the time of diagnosis. We also identified patients with serum CRP and ESR levels greater than 3 mg/L and ≥15 mm/1st hour respectively at diagnosis. Data on traditional CV risk factors and CV events (ischemic heart disease, congestive heart failure, ischemic stroke, and peripheral artery disease) were also assessed.

Two clinical indexes of disease activity (Bath Ankylosing Spondylitis Disease Activity Index, BASDAI, and Ankylosing Spondylitis Disease Activity Score, ASDAS), a functional status index (Bath Ankylosing Spondylitis Functional Index, BASFI), a metrologic index (Bath Ankylosing Spondylitis Metrology Index, BASMI), an enthesitis index (Maastricht Ankylosing Spondylitis Enthesitis Score -MASES) [11–15], and the presence of synovitis were evaluated in all patients at the time of the study. Structural damage was assessed by the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) [16], and the presence of syndesmophytes on spinal radiographs. Patients also underwent a standard anteroposterior plain radiograph of the pelvis to classify the patients as radiographic or nr-axSpA and to assess the degree and symmetry of the radiological sacroiliitis.

Serum levels of CRP, ESR, and lipids at the time of recruitment were reviewed, and information about waist circumference, maximum body mass ndex, and blood pressure was also obtained. The risk of CV disease was estimated by calculating the updated SCORE in all patients 40 years of age or older without CV events, diabetes, or chronic kidney disease [17]. With respect to this, the 2021 European Society of Cardiology Guidelines on CV disease prevention in clinical practice proposed three risk categories (low to moderate, high, and very high), each of one using different numerical cutoff levels depending on different age groups (<50, 50–69, and ≥70 years). SCORE2 estimates an individual's 10-year risk of fatal and non-fatal CV disease events in individuals aged 40 to 69 years. For healthy people aged ≥70 years, the SCORE2-OP (older persons) algorithm estimates 5-year and 10-year fatal and non-fatal CV disease events

We obtained a subject's written consent in all the cases. The study was approved by the Ethics Committee of Hospital Universitario Marques de Valdecilla (Santander, Spain) and subsequently by Ethics Committees of the other Spanish centers.

Carotid ultrasound examination

Carotid ultrasound (US) examination was performed according to the same protocol in the participating hospitals, following the Mannheim carotid intima-media thickness (IMT) and plaque consensus (2004–2006–2011) [18]. It included the measurement of carotid IMT in the common carotid artery and the detection of focal plaques in the extracranial carotid tree following the Mannheim consensus. Plaque was defined as a focal protrusion at least carotid IMT>1.5 mm in the lumen, protrusion at least 50% greater than the surrounding carotid IMT, or arterial lumen encroaching >0.5 mm. The carotid IMT was determined as the average of three measurements in each common carotid artery and the final carotid IMT was the largest average carotid IMT (left or right).

Statistical analysis

Demographic and clinical characteristics in patients with axSpA were described as mean (standard deviation) or percentage (numbers) for categorical variables. For non-normally distributed continuous variables, data were expressed as median and interquartile range (IQR). Univariable differences between different axSpA subgroups were assessed through the Student's T, Mann–Whitney U, Chi2 or Fisher's exact tests according to normal distribution or number of subjects. Association of axSpA disease-related data with carotid IMT and plaque was performed through, respectively, multivariable linear and logistic regression analysis. The confounders were selected from the demographic-related data that had a univariable difference between sexes with a *p*-value less than 0.20. Besides, any other variables that for clinical reasons could be considered as confounding were included in the multivariable analyses. All the analyses used a 5% two-sided significance level and were performed using Stata software, version 17/SE (StataCorp, CollegeStation, TX, USA). P-values <0.05 were considered statistically significant.

Results

611 men and 301 women were recruited for this study.

Sex differences in disease-related features

The main disease-related characteristics of men and women patients are summarized in Table 1. Compared to women, the men group was characterized by a higher r-axSpA: nr-axSpA ratio (514/97 versus 205/94, $p<0.001$) and a longer duration of the disease 15 [8–26] versus 11 [5–21] years, $p=<0.001$).

Men showed hip involvement (19% versus 11%, $p = 0.002$) and psoriasis (13% versus 7%, $p = 0.008$) more frequently than women, whereas women had higher levels of ESR at diagnosis (16 [9–29] versus 11 [5–26] mm/1st hour, $p = 0.038$) and more frequently values of ESR≥15 mm/1st hour (55% versus 41%, $p<0.001$).

At the time of the study, women exhibited a higher disease activity measured by ASDAS (2.45 ± 1.03 versus 2.25 ± 1.02, $p = 0.012$) and BASDAI (4.5 [2.7–6.0] versus 3.3 [1.6–5.2], $p=<0.001$), more commonly punctuation of BASDAI>4 (61% versus 40%, $p<0.001$), more severe back pain (VAS: 4.5 ± 2.5 versus 3.9 ± 2.5, $p = 0.001$) and higher MASES (0 [0–4] versus 0 [0–1], $p=<0.001$). Women also had asymmetric sacroiliitis in a higher proportion (21% versus 15%, $p = 0.02$). In contrast, men showed higher radiological damage measured by mSASSS (7 [1–22] versus 3 [0–7], $p=<0.001$), presence of syndesmophytes (50% versus 19%, $p<0.001$) and severe sacroiliitis (66% versus 42%, $p<0.001$) compared to women. Men also showed worse mobility limitation measured by BASMI (2.86 ± 2.19 versus 2.52 ± 1.75, $p = 0.033$), without differences between both sexes with respect to the BASFI. We also observed significant differences in the treatments used at the time of the study: women received more NSAIDs (86% versus 78%, $p = 0.003$) and DMARDs (44% versus 32%, $p<0.001$), while TNF inhibitors were more frequently used in men (42% versus 25%, $p<0.001$). Except for BASMI and asymmetric sacroiliitis, all observed differences in disease characteristics at the time of the study remained statistically significant after adjustment for confounding factors.

Table 1
Main sociodemographic, clinical, laboratory and radiological characteristics in men and women with axSpA.

Variable	Men	Women	Univariable P value	Multivariable*
	611	301		
Mean age ±SD at the time of study, years	49 ± 13	49 ± 13	0.72	
r-axSpA/nr-axSpA	**514/97**	**205/94**	**<0.001**	
Mean disease duration, years since first symptoms	**15 (8–26)**	**11 (5–21)**	**<0.001**	
Historical disease related data				
Diagnosis delay, years	2 (0–8)	2 (0–7)	0.49	
History of peripheralarthritis, n (%)	214 (35)	112 (38)	0.48	
History of enthesitis, n (%)	178 (29)	101 (34)	0.14	
History of dactilitis, n (%)	34 (6)	24 (8)	0.15	
History of hip involvement, n (%)	**113 (19)**	**32 (11)**	**0.002**	
Extraarticular manifestations, n (%)				
Uveitis, n (%)	123 (20)	58 (20)	0.81	
Inflammatory Bowel Disease, n (%)	43 (7)	18 (6)	0.56	
Psoriasis, n (%)	**81 (13)**	**22 (7)**	**0.008**	
HLA-B27 positive, n (%)	428 (74)	208 (72)	0.57	
CRP at time of disease diagnosis, (mg/dL)	5.0 (1.4–14.6)	4.0 (1.0–11.0)	0.094	
CRP >3 at time of diagnosis	327 (56)	159 (56)	0.98	
ESR at the time of disease diagnosis (mm/1st hour)	**11 (5–26)**	**16 (9–29)**	**0.038**	
ESR ≥15 at the time of disease diagnosis (mm/1st hour)	**198 (41)**	**138 (55)**	**<0.001**	
Disease related data at time of study				
ASDAS	**2.25 ± 1.02**	**2.45 ± 1.03**	**0.012**	**0.014**
Inactive disease (<1.3)	**94 (17)**	**40 (16)**	**0.002**	
Low disease activity (1.3–2.09)	**153 (29)**	**45 (18)**		
High disease activity (2.1–3.5)	**222 (42)**	**138 (55)**		
Very high disease activity (>3.5)	**55 (11)**	**30 (12)**		
BASDAI	**3.3 (1.6–5.2)**	**4.5 (2.7–6.0)**	**<0.001**	**<0.001**
BASDAI>4	**236 (40)**	**167 (61)**	**<0.001**	**<0.001**
BASFI	3.5 ± 2.6	3.7 ± 2.5	0.35	
BASFI≥3.8	238 (42)	124 (46)	0.26	
Back pain (VAS)	**3.9 ± 2.5**	**4.5 ± 2.5**	**0.001**	**0.003**
BASMI	**2.86 ± 2.19**	**2.52 ± 1.75**	**0.033**	0.73
MASES	**0 (0–1)**	**0 (0–4)**	**<0.001**	**<0.001**
Peripheral arthritis	214 (35)	112 (38)	0.48	
Syndesmophytes	**286 (50)**	**51 (19)**	**<0.001**	**<0.001**
mSASSS	**7 (1–22)**	**3 (0–7)**	**<0.001**	**0.013**
Severe sacroiliitis (grade 3 or 4)	**394 (66)**	**120 (42)**	**<0.001**	**0.049**
Asymetric sacroiliitis	**88 (15)**	**60 (21)**	**0.020**	0.16
Current treatment				
NSAIDs, n (%)	**471 (78)**	**258 (86)**	**0.003**	**0.012**
Prednisone, n (%)	76 (13)	43 (14)	0.46	
DMARDs, n (%)	**196 (32)**	**133 (44)**	**<0.001**	**0.004**
Anti-TNF-alpha, n (%)	**253 (42)**	**76 (25)**	**<0.001**	**<0.001**

* Adjusted for r-axSpA/nr-axSpA, disease duration, history of enthesitis, dactylitis and hip involvement, psoriasis, current or past smoking, and CRP and ESR at diagnosis.

Sex differences in cardiovascular features

Table 2 shows the comparison of CV data between men and women patients with axSpA.

A history of smoking (31% versus 25%, $p = 0.033$), hypertension (30% versus 22%, $p = 0.009$), and dyslipidemia (36% versus 28%, $p = 0.015$) were more frequently observed in men than in women. The group of men also had a more deleterious lipid profile at the time of the study, with lower serum HDL cholesterol levels and a higher atherogenic index (50 ± 13 versus 62 ± 18 mg/dl, $p=<0.001$ and 4.00 ± 1.14 versus 3.3 ± 0.99, $p=<0.001$, respectively), higher serum levels of triglycerides (129 ± 88 versus 106 ± 65 mg/dl, $p=<0.001$) and a more frequent prescription of statins (22% versus 13%, $p = 0.004$). The mean systolic (132 ± 17 versus 126 ± 18 mm Hg, $p<0.001$) and diastolic (81 ± 11 versus 77 ± 10, $p<0.001$) blood pressure values were also higher in men, as occurred with the mean waist circumference (62 ± 18 versus 50 ± 13 mm Hg, $p=<0.001$), although women showed more frequently abnormally high values of waist circumference (49% versus 32%, $p<0.001$).

CV disease was more severe in men, who showed more commonly history of CV events (6% versus 2%, $p = 0.008$), more frequently carotid plaques (37% versus 26%, $p = 0.001$), and higher values of carotid IMT (0.665 ± 0.149 versus 0.609 ± 0.129 mm, $p=<0.001$). However, after adjustment for traditional CV risk factors, only results related to carotid IMT remained statistically significant.

Sex differences in potential pro-atherogenic factors

We performed this procedure to determine the possible association between atherosclerosis assessed by carotid ultrasound and factors related to the disease in both gender groups, highlighting those characteristics of axSpA with different predominance in men and women (Table 3).

A history of smoking, obesity, and hypertension were significantly associated with carotid plaques and carotid IMT in men. Hypertension in women was also significantly associated with carotid plaques or carotid IMT. In contrast, dyslipidemia was associated with carotid plaques and carotid IMT in men, but only with carotid IMT in women. Furthermore, high waist circumference was significantly associated with carotid IMT in both sexes (Table 3).

Disease duration, BASFI, BASMI, and mSASSS were associated with carotid plaques and carotid IMT in both men and women. Association of CRP and ESR serum levels at the time of diagnosis with carotid IMT was also observed regardless of sex (Table 3). While ASDAS, BASDAI, and back pain were associated with both carotid plaques and carotid IMT in men, a statistically significant association between psoriasis and carotid plaques was only found in women (Table 3).

Sex differences in carotid plaques and axSpA features among patients categorized in the same level of CV risk according to the SCORE2/SCORE-OP

To establish if the clinical features of the disease could lead to sex differences in the CV disease burden, we first compared the prevalence of carotid plaques in men and women with the same level of CV risk stratified according to the SCORE/SCORE-OP (Table 4). Following this procedure, any differences in this comparison could be explained by sex differences in proatherogenic factors other than age and classic CV risk factors, which are included in the SCORE assessment. In this sense, the men included in the SCORE category of low-moderate CV risk had more carotid plaques (32% vs. 23%, $p = 0.050$). In contrast, within the high-very high risk SCORE category, carotid plaques were seen more frequently in women (70% vs. 49%, $p = 0.028$).

We also analyzed the disease profile of men and women with AxSpA included in the same level of CV risk category according to the SCORE. In this regard, men included in the low-moderate CV risk group were characterized by longer disease duration (19 ± 11 versus 15 ± 11 years, $p = 0.004$), higher mSASSS (8 [2–18] versus 4 [1–8], $p = 0.001$), and more frequent concomitant psoriasis (14% versus 7%, $p = 0.023$) than women. Higher disease activity measured by BASDAI (4.4 ± 2.2 versus 3.3 ± 2.4, $p=<0.001$), ASDAS (2.4 ± 1.0 versus 2.1 ± 1.1, $p = 0.018$), and back pain (4.7 ± 2.4 versus 3.7 ± 2.4, $p<0.001$) were more commonly observed in women with axSpA and low-moderate SCORE.

In addition to a more active disease according to the ASDAS and BASDAI indices, the women included in the high-very high CV risk category according to the SCORE presented higher ESR levels at diagnosis [23 (13–44) versus 14 (7–28), $p = 0.007$] and a greater functional

Table 2
Main cardiovascular data in men and women with axSpA.

Variable	Men	Women	Univariable p	Multivariable* Beta coef./OR (95% CI) p
Mean age ±SD at the time of study, years	49 ± 13	49 ± 13	0.72	
History of Cardiovascular risk factors, n (%)				
Current smoker	**192 (31)**	**74 (25)**	**0.033**	
Hypertension	**183 (30)**	66 (22)	**0.009**	
Dyslipidemia	**221 (36)**	**85 (28)**	**0.015**	
Obesity	140 (23)	70 (24)	0.94	
Diabetes mellitus	51 (8)	16 (5)	0.099	
Chronic kidney disease	15 (2)	4 (1)	0.26	
Lipids, mg/dl				
Total cholesterol	189 ± 40	194 ± 39	0.092	
HDL-cholesterol	**50 ± 13**	**62 ± 18**	**<0.001**	
LDL-cholesterol	116 ± 34	112 ± 31	0.11	
Atherogenicindex ≥4	**4.00 ± 1.14**	**3.3 ± 0.99**	**<0.001**	
Triglycerides	**129 ± 88**	**106 ± 65**	**<0.001**	
Statin intake, n (%)	**118 (22)**	**35 (13)**	**0.004**	
Bloodpressure, mm Hg				
Systolic	**132 ± 17**	**126 ± 18**	**<0.001**	
Diastolic	**81 ± 11**	**77 ± 10**	**<0.001**	
Body mass index	**27 ± 4**	**27 ± 6**	**0.012**	
Waist circumference, (cm)	**98 ± 13**	**89 ± 14**	**<0.001**	
High waist circumference[1], n (%)	**173 (32)**	**130 (49)**	**<0.001**	
CV disease/ atheroclerosis				
Carotid plaques, n (%)	**221 (37)**	**74 (26)**	**0.001**	0.98 (0.64–1.49), 0.93
Carotid intima-media thickness, mm	**0.665 ± 0.149**	**0.609 ± 0.129**	**<0.001**	**−0.030 (−0.052- −0.008), 0.007**
Cardiovascular events, n (%)	**36 (6)**	**6 (2)**	**0.008**	0.41 (0.11–1.49), 0.18

[1] Waist circumference >102 cm in men and >88 cm in women.
* adjusted for smoking, hypertension, dyslipidemia, statins, BMI, waist circumference and diabetes mellitus

Gender is the independent variable in the multivariable linear regression analysis (male reference variable)

Beta coefficients and odds ratio -OR- are shown in the multivariable analysis.

Table 3
Cardiovascular and disease-related factors associated with atherosclerosis in men and women with axSpA.

	MEN		WOMEN	
	Carotid plaques, OR (95% CI), p*	IMT, beta coefficient (95%CI), p**	Carotid plaques, OR (95% CI), p*	IMT, beta coefficient (95%CI), p**
Cardiovascular features				
Have ever smoked	**1.83 (1.27–2.64), 0.001**	**49 (26–73), <0.001**	0.99 (0.56–1.73), 0.97	´−16 (−47–13), 0.27
Obesitty	**1.57 (1.04–2.36), 0.03**	**52 (24–81), <0.001**	1.37 (0.74–2.54), 0.32	**42 (7–77), 0.02**
Hypertension	**2.57 (1.77–3.72), <0.001**	**108 (84–133), <0.001**	**2.12 (1.16–3.92), 0.02**	**87 (52–122),<0.001**
Dyslipidemia	**1.96 (1.31–2.95), 0.001**	**71 (46–95), <0.001**	1.03 (0.52–2.04), 0.94	**76 (44–108), <0.001**
HDL-cholesterol	1.003 (0.99–1.02), 0.61	´−0.38 (−1–0.5), 0.40	0.99 (0.97–1.003), 0.13	´−0.46 (−1- −0.4), 0.28
LDL-cholesterol	1.001 (0.99–1.00), 0.60	**0.37 (0.01–0.7), 0.04**	0.99 (0.99–1.01), 0.59	**0.58 (0.1–1), 0.02**
Atherogenic index ≥4	1.16 (0.81–1.67), 0.42	18 (−5–42), 0.13	0.64 (0.31–1.30), 0.22	5.97 (−31–43), 0.75
Triglycerides	1.00 (0.99–1.00), 0.76	**0.13 (−0.02–0.3), 0.05**	1.00 (0.99–1.00), 0.19	0.20 (−0.3–0.4), 0.09
High waist circumference	1.38 (0.93–2.03), 0.11	**61 (35–88), 0.00**	1.43 (0.79–2.56), 0.23	**63 (33–94), <0.001**
Diseaserelatedfeatures				
Disease duration	**1.05 (1.04–1.07), <0.001**	**4 (3–4), <0.001**	**1.05 (1.03–1.08), <0.001**	**4 (3–5), <0.001**
CRP at diagnosis	1.01 (1.00–1.01), 0.12	**0.84 (0.36–1), 0.001**	1.01 (1.00–1.02), 0.20	**0.75 (0.07–1), 0.03**
ESR at diagnosis	1.01 (1.00–1.02), 0.06	**1 (0.54–2), <0.001**	**1.02 (1.01–1.04), 0.001**	**2 (1–3), <0.001**
BASFI	**1.18 (1.10–1.26), <0.001**	**12 (8–17), <0.001**	**1.22 (1.08–1.38), 0.001**	**7 (1–13), 0.02**
BASMI	**1.32 (1.20–1.46), <0.001**	**16 (11–22), <0.001**	**1.27 (1.07–1.51), 0.006**	**20 (11–28),<0.001**
mSASSS	**1.02 (1.01–1.04), <0.001**	**2 (1–3), <0.001**	**1.04 (1.00–1.08), 0.04**	**3 (2–5), <0.001**
MASES	1.04 (0.94–1.15), 0.44	0.03 (−7–7), 0.99	0.95 (0.86–1.05), 0.37	1 (−4–6), 0.70
Psoriasis	1.12 (0.67–1.86), 0.67	31 (−5–65), 0.09	**2.65 1.00–6.97), 0.05**	´−3 (−59–52), 0.91
BASDAI	**1.11 (1.02–1.20), 0.01**	**8 (3–14), 0.002**	1.12 (0.98–1.28), 0.08	1 (−5–8), 0.68
ASDAS	**1.25 (1.04–1.50), 0.02**	**20 (8–32), 0.001**	1.28 (0.95–1.72), 0.10	6 (−9–22), 0.41
Back pain (VAS)	**1.10 (1.02–1.19), 0.01**	**8 (3–13), 0.003**	1.09 (0.96–1.23), 0.17	1 (−5–8), 0.68
Current NSAIDs	0.79 (0.53–1.19), 0.27	**´−31 (−60–2), 0.04**	0.62 (0.30–1.28), 0.19	**´−67 (−110–24), 0.003**
Current TNF-i	0.81 (0.57–1.15), 0.24	23 (−2–47), 0.07	1.05 (0.57–1.94), 0.88	**45 (11–79), 0.009**
Current DMARDs	**1.54 (1.07–2.23), 0.02**	**29 (3–54), 0.003**	0.98 (0.56–1.71), 0.96	13 (−17–43), 0.39

adjusted by age and smoking.
IMT: Intima-Media Thickness.
* In 779 patients older than 35 years.
** In 908 axSpA patients older than 18 years.

Table 4
Sex differences in carotid plaques and axSpA features among men and women patients with axSpA categorized in the same level of cardiovascular risk according to the SCORE2/ SCORE-OP*.

	Low-moderate CV risk			high-very high CV risk		
	Men (n = 159)	Women (n = 153)	p	Men (n = 187)	Women (n = 34)	p
Prevalence of carotid plaques, n (%)	**51 (32)**	**34 (23)**	**0.050**	**91 (49)**	**23 (70)**	**0.028**
Disease related features						
Disease duration, years	**19 ± 11**	**15 ± 11**	**0.004**	21 ± 12	22 ± 12	0.72
CRP at diagnosis, mg/l	5.8 (1.3–17.2)	3.3 (1.0–9.9)	0.071	5.8 (2.4–17.5)	5.0 (1.6–18.0)	0.88
ESR at diagnosis, mm/1st hour	11 (4–28)	16 (8–29)	0.34	**14 (7–28)**	**23 (13–44)**	**0.007**
BASFI	3.4 ± 2.5	3.6 ± 2.3	0.45	**4.0 ± 2.8**	**5.4 ± 2.9**	**0.011**
BASMI	3.0 ± 2.2	2.6 ± 1.7	0.071	3.3 ± 2.2	3.6 ± 1.7	0.43
mSASSS	**8 (2–18)**	**4 (1–8)**	**0.001**	18 (4–38)	9 (3–21)	0.40
Psoriasis, n (%)	**23 (14)**	**10 (7)**	**0.023**	21 (11)	1 (3)	0.054
BASDAI	**3.3 ± 2.4**	**4.4 ± 2.2**	**<0.001**	**3.6 ± 2.2**	**5.2 ± 2.4**	**<0.001**
ASDAS	**2.1 ± 1.1**	**2.4 ± 1.0**	**0.018**	**2.4 ± 1.0**	**2.9 ± 1.1**	**0.027**
Back pain (VAS)	**3.7 ± 2.4**	**4.7 ± 2.4**	**<0.001**	4.1 ± 2.4	5.0 ± 2.9	0.076

* For patients > 40 years old and without CV events, diabetes or chronic kidney disease.
CV: cardiovascular.

limitation measured by BASFI (5.4 ± 2.9 versus 4.0 ± 2 0.8, $p = 0.011$), with no significant sex differences in disease duration, CRP values, mSASSS or BASMI (Table 4).

Discussion

The present study analyzes for the first time the sex differences in the CV risk characteristics of patients with axSpA. In our series, as in the general population [19,20], men were found to have a more severe atherosclerotic disease compared with women. In this regard, in addition to a higher prevalence of CV events, they had more carotid plaques and higher carotid IMT values, two well-recognized surrogate markers of subclinical atherosclerosis associated with increased CV risk [21].

Men also presented a greater burden of classic risk factors. Waist circumference at the time of study was also higher in men, as was the case with total cholesterol, LDL-cholesterol, and triglycerides, although only the latter reached statistical significance. These differences were comparable to those reported in different Spanish population-based studies carried out in the first decade of the 21st century. [10]. Therefore, the greater atherosclerotic burden observed in the group of men with AxSpA seems to be largely explained by the higher presence of classic risk factors, as suggested by the loss of statistical significance after adjusting for smoking, hypertension, dyslipidemia, statins, BMI, waist circumference and diabetes mellitus. However, the Framingham study reported that the sex difference in the incidence of coronary heart disease could not be fully explained by classic risk factors (cholesterol, blood pressure, diabetes, smoking) [22]. In this regard, men have previously been associated with an increased risk of carotid plaques

independent of classic CV risk factors [23,24].

In addition to analyzing traditional CV risk factors, we also assessed the potential influence of sex differences in axSpA manifestations on the CV risk in our cohort. Women were characterized by higher levels of ESR at diagnosis and a more active disease measured by ASDAS and BASDAI, while men showed a longer disease duration, more radiographic damage, worse mobility limitation, and a more prevalence of psoriasis. These results coincide with those obtained in previous studies [2], except for the prevalence of psoriasis, which in general has been found to be higher in women [25–27] and for the ASDAS values, which did not exhibit sex differences either in the prospective DESIR cohort [28] or in the multinational multicenter ASAS-perSpA study [27]. Remarkably, all the aforementioned differentiating features were associated with subclinical atherosclerosis in our series, thus potentially leading to sex differences in the atherosclerosis burden. Supporting this hypothesis, we found differences in atherosclerosis severity of men and women with comparable CV risk conferred by age and classic CV risk factors but who nevertheless exhibited significant differences in some features of axSpA associated with carotid plaques or carotid IMT. In this regard, within the low-moderate CV risk category according to SCORE, men showed more carotid plaques along with longer disease duration and higher mSASSS, psoriasis, BASMI and CRP levels, although the increase in the latter two did not show statistical significance. However, among patients with high-very high CV risk according to SCORE, carotid plaques were observed more frequently in women with axSpA, who had more active disease according to the ASDAS and BASDAI indices, higher ESR levels at diagnosis and greater functional limitation as measured by BASFI.

It is well known that the increased CV risk that characterizes chronic inflammatory diseases is mainly related to the interaction between the increased incidence of classic CV risk factors and the proatherogenic effect of chronic inflammation [29]. In our series, the different disease profile presented by men and women with axSpA and high-very high CV risk according to the SCORE suggests that this interaction could be especially close among women, thus determining a more severe atherosclerosis in the subgroup of women with high CV risk. This hypothesis is supported by the results of previous studies that also reported sex-related differences in the relationship between inflammatory markers and classical CV factors. In this sense, a study carried out by Rubio-Vargas et al. on 428 patients with SpA found a correlation between BMI and CRP levels only in female patients [30]. Of note, similar findings showing a stronger association between inflammation and obesity in women in the general population were also reported [31]. Sex-based differences in the relationship between CRP and total cholesterol, low-density lipoprotein, and triglycerides were also found in a study that included 165 healthy subjects, 90 men and 75 women [32]. Furthermore, in a recent study from Norway analyzing 3280 patients, higher CRP levels were associated with higher blood pressure and new-onset hypertension only in women and independent of BMI, also suggesting a sex-specific interaction between inflammation and blood pressure [33]. The pathophysiological mechanisms for these sex differences remain unclear, although the well-documented differences in body fat distribution and systemic sex hormone concentrations can explain these findings [34]. In addition, sex-specific associations between inflammation and classic CV risk factors could help explain the results of studies showing sex differences in increased CV risk among patients with different inflammatory conditions. With respect to AS, the British Clinical Practice Research Data Link reported a trend towards an increased risk of developing ischemic heart disease exclusively in female patients [6], whereas a study comparing 1791 hospitalized AS patients with a group of 8955 matched controls confirmed a higher risk for all-cause death in women compared to men [2.38 (1.91, 2.89) versus 1.60 (1.35, 1.90) respectively] [35]. Regrettably, this study did not show sex-specific data on CV disease. Interestingly, Goodson et al. also reported differences by sex in CV mortality in seropositive patients with early arthritis, only finding a significant increase in the female group [36]. In the same line, congestive heart failure tended to be increased in women compared with men in a population-based study of patients with rheumatoid arthritis [37]. Stronger associations between psoriasis, CV risk factors, and atherosclerotic cardiovascular disease have also been reported in psoriatic women compared with men [38].

The limitations of our study include its cross-sectional design, which cannot determine the nature of the relationship between disease manifestations, including inflammatory markers, and traditional CV risk factors. The multicenter design could be another limitation, mainly in terms of the collection of surrogate markers of atherosclerosis. However, the US examination was performed in all cases by rheumatologists trained in ultrasonography, all of them following the same Mannheim criteria to minimize variability.

In conclusion, men with axSpA have more severe atherosclerosis than women, mainly due to a higher burden of classic CV risk factors. However, we have identified some sex differences in the degree of inflammation and disease severity, which are associated with subclinical atherosclerosis and could impact CV risk in men and women with axSpA. This may be especially applicable to women at high CV risk based on risk chart algorithms, as they show higher disease activity and more severe subclinical atherosclerosis than men, suggesting a stronger interaction between inflammation, classic CV risk factors and atherosclerosis in women with axSpA. In addition, our results raise our concern about the need for adequate primary prevention of CV disease in women with axSpA with high-very high CV risk according to SCORE due to the high frequency of carotid plaques, which implies a high risk of CV events.

Declaration of Competing Interest

None.

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