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ORIGINAL RESEARCH

Sex-specific impact of inflammation on traditional cardiovascular risk factors and atherosclerosis in axial spondyloarthritis. A multicentre study of 913 patients

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ABSTRACT

Introduction The nature of the relationship between inflammation, cardiovascular (CV) risk factors and atherosclerosis in axial spondyloarthritis (axSpA) remains largely unknown and sex differences in this regard are yet to be assessed.

Methods Study including 611 men and 302 women from the Spanish multicentre AtheSpAin cohort to assess CV disease in axSpA. Data on CV disease risk factors were collected both at disease diagnosis and at enrolment, and data on disease activity, functional indices and carotid ultrasonography only at enrolment.

Results After a median disease duration of 9 years, patients of both sexes who at disease diagnosis had elevated acute phase reactants (APRs), more frequently had hypertension and obesity. The same occurred with dyslipidaemia in men and with diabetes mellitus in women. At enrolment, CV risk factors were independently associated with APR and with activity and functional indices, with various sex differences. C reactive protein (CRP) values were inversely associated with HDL-cholesterol in men (β coefficient: −1.2 (95% CI: −0.3 to −0.07) mg/dL, p=0.001), while erythrocyte sedimentation rate values were positively associated with triglycerides in women (β coefficient: 0.6 (95% CI: 0.04 to 1) mg/dL, p=0.035). Furthermore, only women showed an independent relationship between insulin resistance parameters and APR or disease activity. Both men and women with high–very high CV risk according to the Systematic Assessment of Coronary Risk Evaluation 2 and CRP levels higher than 3 mg/L at diagnosis of the disease presented carotid plaques significantly more frequently than those with normal CRP levels at disease diagnosis.

Conclusion Inflammation is associated with atherosclerosis and CV disease in axSpA. A gender-driven effect is observed in this relationship.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Inflammation appears to play a key role in the atherosclerosis of inflammatory rheumatic diseases, acting both through and independently of classic cardiovascular (CV) risk factors.

⇒ However, this point has not been definitively established in patients with axial spondyloarthritis (axSpA) and possible sex differences in this regard have not yet been evaluated.

INTRODUCTION

Immune-mediated inflammatory diseases (IMIDs) are a group of conditions that share common inflammatory pathways with immune dysregulation and are characterised by an increased risk of various comorbidities, including cardiovascular (CV) disease.[1 2]

Systemic inflammation plays a key role in the CV risk of IMIDs. It has been hypothesised that proinflammatory cytokines, in addition to having a deleterious effect on the vascular

WHAT THIS STUDY ADDS

⇒ Inflammatory activity in axSpA is independently associated with parameters related to traditional CV risk factors, and patients with elevated serum levels of acute phase reactants (APRs) have a higher frequency of classic CV risk factors.

⇒ For the first time, we describe notable sex differences in this regard. Serum APR levels and disease activity indices were independently associated with HDL-cholesterol in men and triglyceride and with parameters related to insulin resistance only in women.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our results emphasise the importance of identifying and controlling classic CV risk factors, especially in patients with high baseline serum APR levels, and highlight the need to achieve tight control of inflammation to minimise CV.

⇒ The sex differences identified in this regard could help explain the greater excess CV risk that is usually observed in women with inflammatory diseases and may contribute to achieving a more individualised management of CV risk in these patients.

endothelium, may confer a proatherogenic effect via traditional CV risk factors.[3] Circulating cytokines, such as tumour necrosis factor-alpha, interleukin (IL)-6 or IL-1, can alter the function of distant tissues, including adipose tissue, skeletal muscle or the liver, thus inducing proatherogenic effects such as insulin-resistance or characteristic dyslipidaemia with low total and HDL cholesterol and high triglycerides.[4] There is also a growing body of research pointing to a critical role for inflammation and immunity in the pathogenesis of hypertension.[5] However, most of the studies supporting this hypothesis have been performed in patients with rheumatoid arthritis (RA),[6] and it is unclear whether comparable inflammation-induced proatherogenic effects also occur in patients with axial spondyloarthritis (axSpA), characterised in most cases by a weaker inflammatory response. In this sense, few studies have evaluated the potential impact of inflammation on traditional risk factors in axSpA, and its association with typical alterations such as insulin resistance,[7] or elevated triglycerides[8] has not been confirmed. In addition, studies evaluating a hypothetical proatherogenic effect of inflammation in axSpA are also scarce and in some cases contradictory. In this regard, while several studies failed to demonstrate the association between inflammation and atherosclerosis,[9–12] a recent analysis of the Spanish multicentre AtheSpAin cohort found an independent association between baseline C reactive protein (CRP) and erythrocyte sedimentation rate (ESR) with carotid intima-media thickness.[13]

Interestingly, the excess CV risk in patients with IMIDs may be higher in women. Compared with the general population, patients with RA,[14] ankylosing spondylitis,[15] psoriatic arthritis[16] or inflammatory bowel disease[17] tend to show a greater increase in CV morbidity and mortality than men. The nature of these findings remains unclear, and sex differences in the proatherogenic effect of inflammation could be involved in these differences. A close association between inflammatory markers and obesity,[18] blood pressure[19] or dyslipidaemia[20] has been reported in healthy women. However, we lack studies evaluating potential sex discrepancies in the relationship between inflammation, traditional CV risk factors and atherosclerosis in inflammatory conditions. Recent findings from the AtheSpAin cohort showed greater disease severity and more severe atherosclerosis in women with axSpA and high CV risk, suggesting a closer relationship between inflammation and CV disease burden in women.[21]

Taking all these considerations into account, the present study aims to evaluate the potential effect of inflammation on classic CV risk factors and atherosclerosis in axSpA, as well as to analyse gender differences in this regard. This analysis seeks to elucidate the excess CV risk observed in female patients with axSpA.

MATERIALS AND METHODS

Patients

This is a study of the AtheSpAin cohort that includes a cross-sectional analysis. For this purpose, consecutive patients older than 18 years who met the radiological definitions of axSpA (r-axSpA) and nr-axSpA according to the Assessment of SpondyloArthritis International Society (ASAS) criteria[22] were recruited over 6 years (2013–2019) in 12 different Spanish hospitals.

We obtained information on CV risk and disease-related characteristics at two different times in the course of the disease. Data regarding serum levels of acute phase reactants (APRs) (CRP and ESR) and the presence of traditional CV risk factors (hypertension, dyslipidaemia, obesity, diabetes mellitus and smoking status) at the time of the disease diagnosis were reviewed from the medical records. Patients were considered to have normal APR at diagnosis if the CRP was <3 mg/L and ESR <15 mm/first hour and increased APR if CRP ≥3 mg/L and/or ESR ≥15 mm/first hour, in agreement with the cut-off values associated with an increased risk of CV events in the general population[23 24]

Besides, we collected comprehensive information on the status of the disease and CV risk parameters of all patients at the time of their enrolment in the study. Serum levels of APR (CRP and ESR), 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)), and a metrological index (Bath Ankylosing Spondylitis Metrology Index (BASMI))[25–28] were evaluated in all patients at the time of enrolment. Patients also underwent a standard anteroposterior plain radiograph of the pelvis to classify the patients as radiographic or nr-axSpA. Disease duration since disease diagnosis was also calculated.

Besides, we obtained information on the presence of traditional CV risk and data on the lipid profile and

glucometabolic parameters at the time of enrolment, including serum levels of glucose, insulin, peptide C and insulin resistance indices such as the Homeostatic model assessment of insulin resistance (HOMA2-IR), and of insulin sensitivity (HOMA2-S), the Quantitative Insulin Sensitivity Check Index (QUICKI) and the triglyceride-glucose (TyG) index . Information about waist circumference, maximum body mass index, blood pressure and smoking status was also collected.

The risk of CV disease was also estimated at enrolment by calculating the updated Systematic Coronary Risk Evaluation (SCORE)2 in all patients 40 years of age or older without CV events, diabetes or chronic kidney disease.[29] 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 cut-off 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 40–69 years. For healthy people aged ≥70 years, the SCORE2-OP (older persons) algorithm estimates 5-year and 10-year fatal and non-fatal CV 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 (approval number 2016.052, Acta 8/2017) and subsequently by Ethics Committees of the other Spanish centres.

Carotid ultrasound examination

Carotid ultrasound (US) examination was performed at the time of enrolment in all patients, according to the same protocol in the participating hospitals, following the Mannheim carotid intima-media thickness (IMT) and plaque consensus (2004–2006–2011).[30] 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 of 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.[30] 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).

Patient and public involvement

Patients were not involved in the design, conduct or dissemination of the present study.

Statistical analysis

Demographic and clinical characteristics in patients with axSpA were described as mean±SD or percentages for categorical variables. For non-normally distributed continuous variables, data were expressed as median and IQR. Univariable differences between men and women patients were evaluated using various statistical tests such as Student's t-test, the Mann-Whitney U test, χ^2 test or Fisher's exact test, chosen based on the normality of distribution or the sample size. Relationships of APR or disease scores with traditional CV risk factors, blood pressure, lipid profile and insulin resistance indices were assessed through multivariable logistic and linear regression analysis. Where appropriate, linear regression multiple imputation was performed to account appropriately for missingness in the predictors with missing values. Confounders were selected from those variables that differed between men and women and based on a clinical criterion. All the analyses used a 5% two-sided significance level and were performed using Stata software, V.17/SE (StataCorp, College Station, Texas, USA). P values<0.05 were considered statistically significant.

RESULTS

A total of 913 patients (611 men and 302 women) with axSpA were included in the present study.

Disease and CV features in male and female patients with axSpA

Data on CV and disease features, including disease status indices and inflammatory markers, are summarised in table 1.

Women with axSpA exhibited more commonly increased ESR values at disease diagnosis (55% vs 41%, p<0.001). They also showed more intense inflammatory activity measured by ASDAS (2.45±1.03 vs 2.25±1.02, p=0.012) and BASDAI (4.5 (2.7–6.0) vs 3.3 (1.6–5.2), p<0.001) at the time of their enrolment in the study. Men, however, showed more impaired spinal mobility assessed by BASMI (2.86±2.19 vs 2.52±1.75, p=0.033).

Regarding CV risk features at the time of enrolment, smoking habit (31% vs 25%, p=0.033), hypertension (30% vs 22%, p=0.009) and dyslipidaemia (36% vs 28%, p=0.015) were more prevalent in men. Consistent with this finding, men were characterised by lower serum HDL-cholesterol levels (50±13 vs 62±18 mg/dL, p<0.001) with a higher atherogenic index (4.00±1.14 vs 3.3±0.99, p<0.001), increased serum levels of triglycerides (129±88 vs 106±65 mg/dL, p<0.001), and higher systolic (132±17 vs 126±18, p<0.001) and diastolic (81±11 vs 77±10, p<0.001) blood pressure values. Although obesity measured by body mass index was comparable in both sexes, high waist circumference was more prevalent in women (49% vs 32%, p<0.001). Regarding insulin resistance, glucose serum levels were higher in men (99±25 vs 94±18 mg/dL, p=0.051), while the TyG index was higher in women (4.7±0.3 vs 4.6±0.3, p=0.004), without differences in the other parameters analysed.

Men exhibited more severe atherosclerosis with a higher frequency of carotid plaques at enrolment (37% vs 26%, p=0.001).

Relationship between the degree of inflammatory response at the time of disease diagnosis and the

Table 1 Disease and CV features in men and women patients with axSpA

Variable	Men (n=611)	Women (n=302)	P value
Mean age (years)±SD at the time of enrolment	49±13	49±13	0.72
Mean disease duration (years)±SD at the time of enrolment	12.86±10.77	10.08±9.77	<0.001
APR at the time of disease diagnosis			
CRP (mg/L)	5.0 (1.4–14.6)	4.0 (1.0–11.0)	0.094
CRP >3 (mg/L)	327 (56)	159 (56)	0.98
ESR (mm/first hour)	11 (5–26)	16 (9–29)	0.038
ESR ≥15 mm/first hour	198 (41)	138 (55)	<0.001
Disease status indices and APR at the time of enrolment			
ASDAS	2.25±1.02	2.45±1.03	0.012
BASDAI	3.3 (1.6–5.2)	4.5 (2.7–6.0)	<0.001
BASDAI >4	236 (40)	167 (61)	<0.001
BASFI	3.5±2.6	3.7±2.5	0.35
BASFI ≥3.8	238 (42)	124 (46)	0.26
BASMI	2.86±2.19	2.52±1.75	0.033
CRP (mg/L)	2.4 (0.7–6.3)	2.1 (0.5–6.0)	0.094
ESR (mm/first hour)	6 (3–13)	9 (4–18)	0.062
CV features at the time of enrolment			
CV risk factors			
Current smoker	192 (31)	74 (25)	0.033
Hypertension	183 (30)	66 (22)	0.009
Dyslipidaemia	221 (36)	85 (28)	0.015
Obesity	140 (23)	70 (24)	0.94
Diabetes mellitus	51 (8)	16 (5)	0.099
Lipids			
Total cholesterol (mg/dL)	189±40	194±39	0.092
High-density lipoprotein (HDL) cholesterol (mg/dL)	50±13	62±18	<0.001
Low-density lipoprotein (LDL) cholesterol (mg/dL)	116±34	112±31	0.11
Atherogenic index*	4.00±1.14	3.3±0.99	<0.001
Triglycerides (mg/dL)	129±88	106±65	<0.001
Statins, n (%)	118 (22)	35 (13)	0.004
Blood pressure, mm Hg			
Systolic	132±17	126±18	<0.001
Diastolic	81±11	77±10	<0.001
BMI	27±4	27±6	0.012
Waist circumference (cm)	98±13	89±14	<0.001
High waist circumference†, n (%)	173 (32)	130 (49)	<0.001
Parameters of insulin resistance			
Glucose, mg/dL	99±25	94±18	0.051
Insulin, U/mL	9.7 (5.6–20.4)	11.2 (5.5–21.3)	0.17
HOMA2-IR, %	1.2 (0.72.7)	1.4 (0.70–2.8)	0.41
HOMA2-S, %	81 (38–141)	69 (36–143)	0.76
Homeostasis Model Assessment (HOMA)2-BC, %	116±83	112±76	0.63
QUICKI	0.34±0.05	0.34±0.06	0.99
C-peptide, ng/mL	1.7 (0.9–3.1)	1.4 (0.7–2.7)	0.24

Continued

Table 1 Continued

Variable	Men (n=611)	Women (n=302)	P value
TyG index	4.6±0.3	4.7±0.3	0.004
Carotid plaques	221 (37)	74 (26)	0.001

*Atherogenic index: total cholesterol/HDL cholesterol.
†Waist circumference >102 cm in men and >88 cm in women.
APR, acute phase reactants; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; BMI, body mass index; CRP, C reactive protein; CV, cardiovascular; ESR, erythrocyte sedimentation rate; HOMA2-IR, Homeostatic model assessment of insulin resistance; HOMA2-S, homeostatic model assessment of insulin sensitivity; QUICKI, Quantitative Insulin Sensitivity Check Index.

frequency of CV risk factors in men and women with axSpA.

Since APR can provide information about the degree of inflammation, we assessed the baseline serum ESR and CRP levels of patients with axSpA at the time of disease diagnosis. These APR may constitute a good expression of the inflammatory load prior to the start of therapy in patients with axSpA. Then, we established two groups of patients: those with normal APR and those with elevated APR at the time of disease diagnosis. Next, we analysed the frequency of traditional CV risk factors both at the time of diagnosis of the disease and at the time of enrolment (table 2).

When assessing classic CV risk factors at diagnosis in those patients with increased basal APR, we observed a higher prevalence of dyslipidaemia and hypertension in both sexes and obesity and diabetes mellitus only in women in comparison with patients with normal APR, although the difference was only statistically significant for dyslipidaemia in men (31% with elevated APR vs 20% with normal APR, p=0.033). However, a stronger relationship was observed between high APR at diagnosis and the presence of traditional CV risk factors at the time of enrolment. Elevated baseline APR was associated with hypertension at enrolment in both sexes (37% vs 19% with normal APR (p<0.001) in men and 28% vs 14% (p=0.026) in women), and with obesity defined as body mass index of 30.0 or greater (37% vs 19% with normal APR (p<0.001) in men and 28% vs 14% (p=0.032) in women). Besides, men with elevated APR at diagnosis also had dyslipidaemia more commonly at the time of enrolment (41% vs 30% in those with normal APR at diagnosis (p=0.042)), whereas women with increased baseline APR showed a higher frequency of diabetes mellitus (10% vs 1% with normal APR, p=0.024).

Table 2 Comparison of the frequency of traditional CVRFs in men and women depending on the degree of inflammation at the time of disease diagnosis

	Frequency of CVRF at the time of diagnosis				Frequency of CVRF at the time of enrolment		
	N	Normal APR at diagnosis, n (%)	Increased APR at diagnosis, n (%)	P value	N	Normal APR at diagnosis, n (%)	Increased APR at diagnosis, n (%)	P value
Hypertension								
Men	57	25 (15)	32 (23)	0.066	90	**34 (19)**	**56 (37)**	**<0.001***
Women	28	8 (10)	20 (21)	0.060	39	**11 (14)**	**28 (28)**	**0.026***
Dyslipidaemia								
Men	80	**35 (20)**	**45 (31)**	**0.033***	115	**53 (30)**	**62 (41)**	**0.042***
Women	36	12 (16)	24 (24)	0.16	52	19 (24)	33 (33)	0.21
Obesity								
Men	22	13 (8)	9 (7)	0.64	90	**34 (19)**	**56 (37)**	**0.047***
Women	21	8 (11)	13 (15)	0.50	39	**11 (14)**	**28 (28)**	**0.032***
Diabetes mellitus								
Men	4	4 (2)	0 (0)	0.13	24	14 (8)	10 (7)	0.61
Women	5	1 (1)	4 (4)	0.31	11	**1 (1)**	**10 (10)**	**0.024***

Normal APR: CRP <3 mg/L and ESR <15 mm/first hour at diagnosis.
Increased APR: CRP >3 mg/L and/or ESR ≥15 mm/first hour at diagnosis.
Values in bold meant that the differences were statistically significant
*P<0.05.
APR, acute phase reactant; CRP, C reactive protein; CVRF, cardiovascular risk factor; ESR, erythrocyte sedimentation rate.

Table 3 Association between ESR and CRP and blood pressure, lipid profile, obesity and insulin resistance parameters at enrolment in men and women with axSpA

		CRP at the time of enrolment, β (p)				ESR at the time of enrolment, β (p)			
		Univariable		Multivariable		Univariable		Multivariable	
CV risk features	Sex	β coefficient (95% CI)	P value	β coefficient (95% CI)	P value*	β coefficient (95% CI)	P value	β coefficient (95% CI)	P value*
Systolic blood pressure (mm Hg)	Men	0.03 (–0.09 to 0.2)	0.597			0.002 (–0.08 to 0.08)	0.946		
	Women	0.2 (–0.1 to 0.5)	0.262			0.1 (–0.02 to 0.3)	0.080	–0.05 (–0.2 to 0.1)	0.552
Diastolic blood pressure (mm Hg)	Men	–0.02 (–0.1 to 0.07)	0.715			–0.02 (–0.07 to 0.03)	0.475		
	Women	0.2 (0.05 to 0.4)	0.011†	0.2 (–0.01 to 0.4)	0.052	0.07 (–0.03 to 0.2)	0.191	0.01 (–0.1 to 0.1)	0.843
Total cholesterol (mg/dL)	Men	–0.2 (–0.50 to 0.08)	0.16	–0.2 (–0.6 to 0.1)	0.19	0.04 (–0.1 to 0.2)	0.65		
	Women	–0.4 (–0.9 to 0.3)	0.25			0.1 (–0.2 to 0.5)	0.45		
LDL-cholesterol (mg/dL)	Men	–0.2 (–0.5 to 0.1)	0.207			0.04 (–0.1 to 0.2)	0.603		
	Women	–0.2 (–0.7 to 0.3)	0.472			–0.07 (–0.3 to 0.3)	0.957		
HDL-cholesterol (mg/dL)	Men	–0.2 (–0.3 to –0.06)	0.001†	**–1.2 (–0.3 to –0.07)**	**0.001***	–0.03 (–0.09 to 0.03)	0.371		
	Women	–0.07 (–0.4 to 0.2)	0.667			–0.1 (–3 to 0.03)	0.105	–0.08 (–2 to 0.1)	0.375
Triglycerides (mg/dL)	Men	–0.04 (–0.3 to 0.2)	0.751			0.3 (–0.06 to 0.7)	0.103	0.2 (–0.4 to 0.8)	0.449
	Women	0.6 (0.2 to 1)	0.002†	1 (–0.3 to 2.2)	0.126	0.6 (0.2 to 1)	0.005†	**0.6 (0.04 to 1)**	**0.035***
Atherogenic index	Men	0.0004 (–0.003 to 0.004)	0.853			0.0003 (–0.005 to 0.006)	0.911		
	Women	0.005 (0.004 to 0.1)	0.036†	–0.004 (–0.02 to 0.1)	0.664	0.01 (0.0004 to 0.1)	0.036†	0.01 (–0.002 to 0.02)	0.129
Body mass index (kg/m^2)	Men	0.03 (–0.00 to 0.06)	0.075	0.12 (0.01 to 0.22)	0.058	0.01 (–0.01 to 0.03)	0.381		
	Women	0.2 (0.07 to 0.3)	<0.001†	**0.1 (0.006 to 0.2)**	**0.038***	0.04 (–0.01 to 0.09)	0.140	0.03 (–0.04 to 0.1)	0.36
Waist circumference (cm)	Men	0.1 (0.05 to 0.2)	0.003†	**0.1 (0.02 to 0.2)**	**0.021***	0.04 (–0.02 to 0.1)	0.180	0.02 (–0.06 to 0.1)	0.50
	Women	0.4 (0.2 to 0.6)	0.001†	0.2 (–0.02 to 0.5)	0.073	0.1 (–0.03 to 0.2)	0.133	0.02 (–0.1 to 0.2)	0.74
Glucose (mg/dL)	Men	–0.05 (–0.3 to 0.2)	0.652			0.03 (–0.1 to 0.2)	0.650		
	Women	0.3 (–0.1 to 0.8)	0.149	0.4 (–0.2 to 0.9)	0.222	–0.06 (–0.3 to 0.1)	0.541		
Insulin (U/mL)	Men	–0.06 (–0.5 to 0.4)	0.754			–0.08 (–0.4 to 0.2)	0.632		
	Women	0.3 (–0.2 to 0.8)	0.232			0.1 (–0.07 to 0.3)	0.228		
C-peptide (ng/mL)	Men	0.02 (–0.006 to 0.04)	0.144	0.01(–0.02 to 0.04)	0.457	0.001 (–0.01 to 0.02)	0.874		
	Women	0.08 (0.02 to 0.1)	0.008†	**0.06 (0.01 to 0.1)**	**0.027***	0.02 (0.002 to 0.03)	0.030†	0.007 (–0.01 to 0.02)	0.42
HOMA2-IR, %	Men	0.001 (–0.03 to 0.03)	0.922			–0.005 (–0.03 to 0.02)	0.675		
	Women	0.04 (0.00 to 0.09)	0.049†	0.04 (–0.01 to 0.09)	0.100	0.01 (–0.009 to 0.03)	0.251		
HOMA2-S, %	Men	–0.6 (–2 to 1)	0.509			–0.3 (–2 to 1)	0.656		
	Women	–3 (–6 to 0.07)	0.056	–2.6 (–5.9 to 0.8)	0.129	–1 (–3 to 0.3)	0.112	–0.8 (–2.5 to 1)	0.381

Continued

Table 3 Continued

CV risk features	Sex	CRP at the time of enrolment, β (p)				ESR at the time of enrolment, β (p)			
		Univariable		Multivariable		Univariable		Multivariable	
		β coefficient (95% CI)	P value	β coefficient (95% CI)	P value*	β coefficient (95% CI)	P value	β coefficient (95% CI)	P value*
QUICKI	Men	−0.000 (−0.001 to 0.000)	0.674			−0.0001 (−0.0006 to 0.0004)	0.61		
	Women	−0.001 (−0.003 to 0.001)	0.087	−0.002 (−0.004 to 0.001)	0.146	−0.0005 (−0.001 to 0.0002)	0.15	−0.0002 (−0.001 to 0.0004)	0.449
TyG index	Men	−0.002 (−0.005 to 0.0007)	0.13	−0.003 (−0.006 to 0.001)	0.17	−0.0001 (−0.002 to 0.002)	0.93		
	Women	0.02 (0.005 to 0.03)	0.003	0.009 (−0.005 to 0.02)	0.20	0.004 (−0.0003 to 0.009)	0.069	0.005 (−0.0007 to 0.01)	0.081

Values in bold meant that the differences were statistically significant.
*Adjusted for confounding factors (age, smoking, statins, TNF-inhibitors, DMARDs, NSAIDs, disease duration, age at diagnosis, r-axSpA/nr-axSpA ratio.
†P<0.05. Columns are independent variables and row are the dependent. Adjustment is only performed for univariable relations who had a p value inferior to 0.20.
axSpA, axial spondyloarthritis; CRP, C reactive protein; CV, cardiovascular; DMARDS, Disease-Modifying Antirheumatic Drugs ; ESR, erythrocyte sedimentation rate; HDL, High-density lipoprotein; HOMA2-IR, homeostatic model assessment of insulin resistance; HOMA2-S, homeostatic model assessment of insulin sensitivity; LDL, Low-density lipoprotein; nr-axSpA, non-radiographic ankylosing spondylitis; NSAIDs, nonsteroidal anti-inflammatory drugs; QUICKI, Quantitative Insulin Sensitivity Check Index; r-axSpA, radiological definitions of axSpA; TNF, tumour necrosis factor; TyG, triglyceride-glucose.

Associations between parameters of CV risk and inflammatory activity, BASMI and BASFI in men and women patients with axSpA at the time of enrolment

Both univariable and multivariable analyses assessing the association between parameters of CV risk and disease features obtained at the time of enrolment were performed for men and women.

Sex differences were observed. In this regard, serum CRP levels obtained at the time of enrolment were independently negatively associated with HDL cholesterol in men (β coefficient: −1.2 (–0.3 to –0.07), p=0.001), whereas women exhibited a significant association between ESR and triglycerides (β coefficient: 0.6 (0.04 to –1), p=0.035). Women also showed a significant association between APR at enrolment and C-peptide (β coefficient: 0.06 (0.01 to 0.1), p=0.027), and a non-significant trend for association with diastolic blood pressure (β coefficient: 0.2 (–0.01 to 0.4), p=0.052) and TyG index (β coefficient: 0.005 (–0.0007 to 0.01), p=0.081). Obesity measured by body mass index or waist circumference was significantly associated with APR at the time in patients of both sexes (table 3).

Association between disease activity at the time of enrolment measured by ASDAS and obesity established according to body mass index and waist circumference in both men (β coefficient: 0.5 (0.1–1), p=0.009 and 2 (1–3), p=0.000, respectively) and women patients (β coefficient: 2 (0.7–2), p=0.001 and 3 (1–5), p=0.003, respectively) was observed (table 4). A sex-specific impact of disease activity on the lipid profile was also found. In this sense, ASDAS and BASDAI were independently associated with HDL cholesterol in men (β coefficient: −3 (−4 to −2), p=0.000 and −0.6 (−1 to −0.03), p=0.039, respectively) and with triglycerides in women (β coefficient: 14 (4–23), p=0.005 and 7 (3–11), p=0.001, respectively). ASDAS at enrolment was also significantly associated with glucose (β coefficient: 4 (0.4–8), p=0.033) and insulin resistance check index QUICKI (β coefficient: −0.02 (−0.03 to −0.004), p=0.001) in women, while BASDAI showed an independent association with systolic (β coefficient: 0.8 (0.1–1), p=0.018) and diastolic blood pressure (β coefficient: 0.8 (0.3–1), p=0.001) in men.

We also analysed the link between CV parameters with BASMI and BASFI, indices measuring mobility and functional limitation (table 5). We confirmed a significant association between both indices and parameters of obesity, lipid profile and insulin resistance in both sexes, although only men showed a significant link with blood pressure in the multivariable analysis.

Differences in the atherosclerotic burden according to the degree of the inflammatory response in men and women with axSpA

We also assessed the severity of atherosclerosis at the time of enrolment in patients with a comparable CV risk based on age and the presence of classic CV risk factors but with different degree of baseline inflammation. For this purpose, we compared the frequency of carotid plaques in men and women patients with axSpA who, being included in the same SCORE CV risk group, had high (>3 mg/L) or low (<3 mg/L) levels of CRP at the diagnosis of the disease (table 6).

Men with low–moderate SCORE and high baseline CRP levels showed a non-significant increase in the frequency of carotid plaques compared with those with low baseline CRP values (30.52% vs 23%, p=0.24). In contrast, women with low–moderate SCORE had the same frequency of plaques (20.8% vs 20.9%, p=0.99).

In line with the above, the comparison between patients without CV risk factors showed a significant increase in carotid plaques in men characterised by a greater inflammatory response (25% vs 11.6%, p=0.006). There was not such a significant difference in women (21.1% vs 15.5%, p=0.39). However, both men and women with high–very high CV risk according to the SCORE had more severe atherosclerosis in the presence of baseline serum CRP levels greater than 3 mg/L (50% vs 35.8%, p=0.045 and 75% vs 33%, p=0.032 respectively).

DISCUSSION

Two decades have now passed since Sattar *et al* proposed a model that explains the mechanisms by which systemic inflammation could have a dual direct and indirect proatherogenic effect in promoting atherosclerosis in RA.[4] The present study supports the validity of this hypothesis in patients with axSpA. First, we found a link between inflammation and classic CV risk factors. The patients in our series showed an independent and statistically significant association between inflammatory activity, measured by APR or activity indices, and multiple CV risk parameters related to blood pressure, lipid profile, insulin resistance and obesity. In addition, those patients who presented a greater inflammatory response at the time of disease diagnosis had a higher frequency of hypertension, dyslipidaemia, obesity and diabetes mellitus at the time of enrolment, years after being exposed to the effect of inflammation.

This close relationship between inflammation and traditional CV risk factors observed in our series is in line with the hypothesis raised by Sattar *et al*, which supports the potential role of inflammation as an inducer of different metabolic disturbances, eventually leading to an increased incidence of classic CV risk factors. Nevertheless, further prospective studies are necessary to confirm this point.

Previous data in this regard are scarce. We had already observed a potential link between disease activity and classic CV risk factors in a previous study from the AtheSpAin cohort,[31] but specific associations with every single risk factor were not assessed. A recent retrospective study also reported an independent link between ESR and an increased risk of incident arterial hypertension in 430 patients with axSpA from Hong-Kong.[32] With respect to dyslipidaemia, an association between APR and total cholesterol and HDL has been found in patients with

Table 4 Association between ASDAS and BASDAI and blood pressure, lipid profile, obesity and insulin resistance parameters at enrolment in men and women with axSpA

		ASDAS, β (p)				BASDAI, β (p)			
		Univariable		Multivariable		Univariable		Multivariable	
CV risk features	Sex	β coefficient (95% CI)	P value	β coefficient (95% CI)	P value*	β coefficient (95% CI)	P value	β coefficient (95% CI)	P value*
Systolic blood pressure (mm Hg)	Men	1 (0.01 to 3)	0.048†	1 (–0.3 to 3)	0.122	0.8 (0.2 to 1)	0.011†	**0.8 (0.1 to 1)**	**0.018**†
	Women	3 (0.6 to 5)	0.013†	0.4 (–2 to 3)	0.730	1 (0.4 to 2)	0.004†	0.3 (–0.7 to 1)	0.561
Diastolic blood pressure (mm Hg)	Men	1 (0.1 to 2)	0.030†	**1 (0.2 to 2)**	**0.024**†	0.7 (0.3 to 1)	0.001†	**0.8 (0.3 to 1)**	**0.001**†
	Women	1 (–0.1 to 2)	0.083	0.3 (–1 to 2)	0.662	0.3 (–0.2 to 0.9)	0.208		
Total cholesterol (mg/dL)	Men	0.8 (–3 to 4)	0.64			1 (–0.1 to 3)	0.059	1 (–0.2 to 3)	0.098
	Women	3 (–2 to 7)	0.23			**2 (0.2 to 4)**	0.032†	1 (–0.9 to 4)	0.24
LDL-cholesterol (mg/dL)	Men	0.8 (–2 to 4)	0.588			0.9 (–0.4 to 2)	0.186	0.7 (–0.7 to 2)	0.348
	Women	2 (–2 to 6)	0.348			0.9 (–0.9 to 3)	0.334		
HDL-cholesterol (mg/dL)	Men	–3 (–4 to –2)	0.001†	**–3 (–4 to –2)**	**0.000***	–0.6 (–1 to 0.1)	0.012†	**–0.6 (–1 to –0.03)**	**0.039**†
	Women	–2 (–4 to 0.2)	0.076	–2 (–4 to 1)	0.202	–0.4 (–1 to 0.6)	0.410		
Triglycerides (mg/dL)	Men	4 (–4 to 11)	0.338			3 (–0.4 to 6)	0.085	3 (–0.9 to 6)	0.135
	Women	17(9–24)	<0.001†	**14(4–23)**	**0.005***	8 (5 to 11)	<0.001†	**7 (3 to 11)**	**0.001**†
Atherogenic index	Men	0.3 (0.2 to 0.4)	<0.001†	**0.3 (0.1 to 0.4)**	**0.000***	0.08 (0.04 to 0.1)	<0.001†	**0.07 (0.03 to 0.1)**	**0.002**
	Women	0.2 (0.07 to 0.3)	0.002†	0.1 (–0.02 to 0.3)	0.085	0.08 (0.03 to 0.1)	0.003†	0.06 (–0.01 to 0.1)	0.090
Body mass index (kg/m^2)	Men	0.6 (0.2 to 1)	0.002†	**0.5 (0.1 to 1)**	**0.009***	0.2 (0.01 to 0.3)	0.040†	0.1 (–0.03 to 0.3)	0.110
	Women	2 (1 to 2)	<0.001†	**2 (0.7 to 2)**	**0.001***	0.5 (0.2 to 0.8)	0.001†	**0.4 (0.04 to 0.8)**	**0.030**†
Waist circumference (cm)	Men	3 (2 to 4)	<0.001†	**2 (1 to 3)**	**0.000***	0.6 (0.1 to 1)	0.018†	0.4 (–0.07 to 1)	0.091
	Women	4 (2 to 6)	<0.001†	**3 (1 to 5)**	**0.003***	1 (0.4 to 2)	0.004†	0.7 (–0.2 to 2)	0.133
Glucose (mg/dL)	Men	0.5 (–3 to 4)	0.744			0.6 (–0.8 to 2)	0.438		
	Women	3 (0.6 to 6)	0.018†	**4 (0.4 to 8)**	**0.033***	1.45 (0.18 to 2.72)	0.026†	1.69 (–0.06 to 3.44)	0.059
Insulin (U/mL)	Men	2 (–4 to 7)	0.539			0.6 (–2 to 3)	0.628		
	Women	4 (0.7 to 7)	0.015†	**3 (–0.8 to 7)**	0.117	1 (0.1 to 3)	0.034†	1.26 (–0.47 to 2.98)	0.151
C-peptide (ng/mL)	Men	0.21 (–0.12 to 0.55)	0.21			0.1 (–0.01 to 0.29)	0.070	0.13 (–0.03 to 0.29)	0.105
	Women	0.56 (0.21 to 0.90)	0.002†	0.3 (–0.06 to 0.7)	0.094	0.2 (0.08 to 0.4)	0.003†	0.11 (–0.07 to 0.29)	0.229
HOMA2-IR, %	Men	0.3 (–0.06 to 0.7)	0.106	0.3 (–0.1 to 0.7)	0.162	1 (–0.07 to 0.3)	0.256		
	Women	0.3 (–0.02 to 0.5)	0.066	0.2 (–0.1 to 0.6)	0.178	0.07 (–0.05 to 2)	0.232		
HOMA2-S, %	Men	–11 (–33 to 11)	0.327			–4 (–14 to 5)	0.371		
	Women	–11 (–28 to 6)	0.211			–2 (–10 to 5)	0.539		

Continued

Table 4 Continued

CV risk features	Sex	ASDAS, β (p)				BASDAI, β (p)			
		Univariable		Multivariable		Univariable		Multivariable	
		β coefficient (95% CI)	P value	β coefficient (95% CI)	P value*	β coefficient (95% CI)	P value	β coefficient (95% CI)	P value*
QUICKI	Men	−0.01 (−0.01 to 0.002)	0.160	−0.002 (−0.01 to 0.01)	0.722	−0.001 (−0.005 to 0.003)	0.511		
	Women	−0.01 (−0.02 to 0.003)	0.017†	**−0.02 (−0.03 to −0.004)**	**0.001†**	−0.003 (−0.01 to 0.001)	0.153	−0.004 (−0.01 to 0.002)	0.143
TyG index	Men	−0.008 (−0.05 to 0.03)	0.70			0.008 (−0.01 to 0.03)	0.38		
	Women	0.02 (−0.03 to 0.08)	0.42			−0.006 (−0.03 to 0.02)	0.66		

Values in bold meant that the differences were statistically significant
*Adjusted for confounding factors (age, smoking, statins, TNF-inhibitors, DMARDs, NSAIDs, disease duration, age at diagnosis, r-axSpA/nr-axSpA ratio.
†P<0.05. Columns are independent variables and rows are the dependent. Adjustment is only performed for univariable relations who had a p value inferior to 0.20.
ASDAS, Ankylosing Spondylitis Disease Activity Score; axSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CV, cardiovascular; HOMA2-IR, homeostatic model assessment of insulin resistance; HOMA2-S, homeostatic model assessment of insulin sensitivity; QUICKI, Quantitative Insulin Sensitivity Check Index; TNF, tumour necrosis factor; TyG, triglyceride-glucose.

AS,[8] while no inflammatory-related disturbances in the glucose metabolism have been reported so far. Interestingly, the link between obesity and inflammation is well-recognised in the general population, but it has largely been related to the consideration of obesity as a subclinical inflammatory condition with adipose tissue releasing hormones and cytokines that contribute to CRP elevation.[33 34] However, patients from our cohort who had displayed elevated APR at diagnosis did not show an increased frequency of obesity at that time compared with patients with normal APR, but they were found to have twice the prevalence of obesity years after, at the time of enrolment. This finding could suggest a more complex bidirectional relationship with inflammation playing a potential role in inducing obesity, a hypothesis that should be confirmed in prospective studies.

Second, we also confirmed an independent proatherogenic effect of inflammation in the patients in our series, regardless of age and traditional risk factors. We found a higher frequency of carotid plaques in those patients who, being categorised in the same level of CV risk according to the SCORE algorithm, presented a higher inflammatory load. Consistent with that, our group previously found an independent relationship between subclinical atherosclerosis and APR even after adjusting for age, sex and traditional CV risk factors.[13] A recent study analysing 10-year retrospective data of a multicentre cohort of 295 patients with axSpA reported a significant association between CV events occurrence and the persistence of increased CRP levels and high disease activity, although in this case the multivariate analysis only included age, sex and diabetes mellitus as confounding factors.[35]

Our study describes for the first-time sex differences in the aforementioned relationship between inflammation and CV risk. The inflammation-related lipid disturbance observed in our patients differed depending on the sex. In this sense, APR and activity indices were significantly associated with HDL-cholesterol and the atherogenic index in men and with triglycerides in women. A previous study including 165 apparently healthy subjects, 90 men and 75 women, also reported an exclusive female association between triglycerides and CRP.[20] Interestingly, a recent meta-analysis showed a decrease in HDL-cholesterol serum levels as the only lipid alteration characterising patients with AS,[36] with no changes in mean triglycerides unlike what happens in other inflammatory rheumatic diseases.[37 38] Our results could explain this discrepancy if we consider the predominance of men who characterises AS. It should be noted that although both the atherogenic index and triglycerides have been shown to be proatherogenic in the general population[2] and in patients with axSpA,[13] triglycerides seem to have a more deleterious CV effect in women.[39]

In our study, the analysis of seven different parameters related to insulin resistance showed a closer link with inflammatory activity in women. Only women showed independent and statistically significant associations between APR or activity indices and parameters such as

Table 5 Association between BASMI and BASFI with blood pressure, lipid profile, obesity and insulin resistance parameters at enrolment in men and women with axSpA

		BASMI, β (p)				BASFI, β (p)			
		Univariate		Multivariate		Univariate		Multivariate	
CV risk features	Sex	β coefficient (95% CI)	P value	β coefficient (95% CI)	P value*	β coefficient (95% CI)	P value	β coefficient (95% CI)	P value*
Systolic blood pressure (mm Hg)	Men	2 (1 to 2)	<0.001†	0.5 (–0.3 to 1)	0.178	1 (0.6 to 2)	<0.001†	**0.6 (0.06 to 1)**	**0.03**†
	Women	3 (2 to 4)	<0.001†	0.5 (–1 to 2)	0.502	2 (1 to 3)	<0.001†	0.7 (–0.3 to 2)	0.180
Diastolic blood pressure (mm Hg)	Men	0.3 (–0.1 to 0.8)	0.176	–0.3 (–0.9 to 0.3)	0.293	0.8 (0.4 to 1)	<0.001†	**0.6 (0.2 to 1)**	**0.002**†
	Women	0.2 (–0.5 to 1)	0.514			0.5 (0.03 to 1)	0.036†	0.2 (–0.4 to 0.8)	0.492
Total cholesterol (mg/dL)	Men	3 (–0.3 to 5)	0.077	0.3 (–3 to 4)	0.88	1 (–0.09 to 2)	0.069	1 (–0.4 to 2)	0.17
	Women	0.4 (–1 to 2)	0.64			1 (–0.6 to 3)	0.17	0.5 (–2 to 3)	0.68
LDL-cholesterol (mg/dL)	Men	–0.2 (–2 to 1)	0.765			0.8 (–0.3 to 2)	0.141	0.8 (–0.4 to 2)	0.209
	Women	3 (0.6 to 6)	0.015†	1 (–2 to 4)	0.433	0.4 (–1 to 2)	0.640		
HDL-cholesterol (mg/dL)	Men	–0.3 (–0.9 to 0.2)	0.242			–0.6 (–1 to –0.2)	0.008†	–0.6 (–1 to –0.1)	**0.013**†
	Women	–1 (–2 to 0.4)	0.175	–1 (–3 to 0.6)	0.191	–0.4 (–1.4 to 0.5)	0.341		
Triglycerides (mg/dL)	Men	3 (–1 to 6.45)	0.166	1 (–4 to 6)	0.649	3 (0.6 to 6)	0.018†	2 (–0.9 to 6)	0.152
	Women	6 (1 to 11)	0.017†	3 (–3 to 10)	0.288	6 (3 to 9)	<0.001†	**5 (0.7 to 9)**	**0.020**
Atherogenic index	Men	0.03 (–0.01 to 0.08)	0.185	0.04 (–0.02 to 0.1)	0.220	0.07 (0.03 to 0.1)	<0.001†	**0.07 (0.03 to 0.1)**	**0.001**†
	Women	0.08 (0.01 to 0.2)	0.029†	0.04 (–0.05 to 0.1)	0.394	0.6 (0.01 to 0.1)	0.010†	0.04 (–0.02 to 0.1)	0.170
Body mass index (kg/m^2)	Men	0.4 (0.2 to 0.6)	<0.001†	**0.2 (0.02 to 0.5)**	**0.030**†	0.3 (0.2 to 0.5)	<0.001†	**0.3 (0.09 to 0.4)**	**0.002**†
	Women	0.5 (0.1 to 1)	0.016†	0.3 (–0.2 to 0.9)	0.220	0.6 (0.3 to 0.9)	<0.001†	**0.5 (0.1 to 0.8)**	**0.009**
Waist circumference (cm)	Men	2 (1 to 2)	<0.001†	**1 (0.6 to 2)**	**<0.001**†	1 (0.8 to 2)	<0.001†	**0.8 (0.4 to 1)**	**0.001***
	Women	3 (2 to 4)	<0.001†	**2 (0.6 to 3)**	**0.003**†	2 (1 to 2)	<0.001†	**1 (0.4 to 2)**	**0.003**
Glucose (mg/dL)	Men	3 (2 to 5)	<0.001†	**2 (0.5 to 4)**	**0.015**†	1.60 (0.40 to 2.80)	0.009†	1 (–0.4 to 3)	0.162
	Women	2 (0.4 to 4)	0.016†	**3 (0.4 to 5)**	**0.022**†	0.71 (–0.41 to 1.83)	0.211		
Insulin (U/mL)	Men	2 (–0.3 to 5)	0.080	0.9 (–2 to 4)	0.566	1.42 (–0.58 to 3.42)	0.163	1 (–1 to 4)	0.375
	Women	1 (–1 to 3)	0.166	0.9 (–2 to 3)	0.463	1.22 (0.08 to 2.36)	0.036†	1 (–0.5 to 3)	0.179

Continued

Table 5 Continued

CV risk features	Sex	BASMI, β (p)				BASFI, β (p)			
		Univariate		Multivariate		Univariate		Multivariate	
		β coefficient (95% CI)	P value	β coefficient (95% CI)	P value*	β coefficient (95% CI)	P value	β coefficient (95% CI)	P value*
C-peptide (ng/mL)	Men	0.2 (0.07 to 0.4)	0.004†	0.1 (–0.08 to 0.3)	0.225	0.13 (–0.001 to 0.26)	0.051	0.1 (–0.05 to 0.3)	0.204
	Women	0.3 (0.07 to 0.5)	0.009†	0.09 (–0.2 to 0.4)	0.499	0.18 (0.04 to 0.32)	0.010†	0.04 (–0.1 to 0.2)	0.616
HOMA2-IR, %	Men	0.3 (0.2 to 0.5)	<0.001†	**0.3 (0.03 to 0.5)**	**0.026**†	0.16 (0.02 to 0.31)	0.022†	0.08 (–0.09 to 0.2)	0.382
	Women	0.1 (–0.05 to 0.3)	0.189	0.05 (–0.2 to 0.3)	0.668	0.07 (–0.04 to 0.18)	0.193	0.03 (–0.1 to 0.2)	0.670
HOMA2-S, %	Men	–12 (–23 to –2)	0.017	–5 (–18 to 9)	0.490	–10.38 (–18.72 to –2.04)	0.015†	–6 (–17 to 4)	0.235
	Women	–5 (–15 to 5)	0.363			–2.63 (–9.47 to 4.20)	0.447		
QUICKI	Men	–0.01 (–0.1 to –0.05)	0.001†	–0.005 (–0.01 to 0.004)	0.072	–0.05 (–0.01 to –0.002)	0.002†	–0.02 (–0.006 to 0.002)	0.247
	Women	–0.01 (–0.01 to 0.0001)	0.062	–0.1 (–0.02 to 0.001)	0.076	–0.03 (–0.007 to 0.001)	0.141	–0.003 (–0.009 to 0.003)	0.263
TyG index	Men	0.02 (0.003 to 0.04)	0.022†	0.03 (0.01 to 0.06)	0.003	0.009 (–0.007 to 0.03)	0.26		
	Women	0.008 (–0.02 to 0.04)	0.61			0.02 (–0.007 to 0.04)	0.18	0.01 (–0.02 to 0.04)	0.38

*Adjusted for confounding factors (age, smoking, statins, TNF-inhibitors, DMARDs, NSAIDs, disease duration, age at diagnosis, r-axSpA/n r-axSpA ratio.
†P<0.05. Columns are independent variables and row are the dependent. Adjustment is only performed for univariable relations who had a p value inferior to 0.20.
axSpA, axial spondyloarthritis; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; CV, cardiovascular; HOMA2-IR, homeostatic model assessment of insulin resistance; HOMA2-S, homeostatic model assessment of insulin sensitivity; nr-axSpA, non-radiographic axSpA ; QUICKI, Quantitative Insulin Sensitivity Check Index; TNF, tumour necrosis factor; TyG, triglyceride-glucose.

Table 6 Frequency of carotid plaques at enrolment in men and women with comparable burden of traditional CV risk factors categorised by the degree inflammation at disease diagnosis

	Men			Women		
	Without any CVRF at enrolment	SCORE low–moderate at enrolment	SCORE high–very high at enrolment	Without CVRF at enrolment	SCORE low–moderate at enrolment	SCORE high–very high at enrolment
CRP <3 mg/L at diagnosis	14/121 (11.6%)	23/100 (23%)	29/81 (35.8%)	11/71 (15.5%)	18/86 (20.9%)	3/9 (33%)
CRP >3 mg/L at diagnosis	32/128 (25%)	29/95 (30.52%)	62/124 (50%)	15/71 (21.1%)	20/96 (20.8%)	15/20 (75%)
P	**0.006**	0.24	**0.045**	0.39	0.99	**0.032**

Values in bold meant that the differences were statistically significant.
CRP, C reactive protein; CV, cardiovascular; CVRF, cardiovascular risk factors; SCORE, Systematic Assessment of Coronary Risk Evaluation.

C-peptide, glucose and QUICKI. In keeping with that, we also observed a non-significant trend with insulin, HOMA2-IR, HOMA2-S and TyG index in women and only with TyG index in men. Supporting the existence of a stronger diabetogenic effect of inflammation in women, only female patients with high APR at diagnosis showed a higher frequency of diabetes mellitus both at that time and at the time of enrolment. This finding could be particularly relevant given the greater impact that diabetes mellitus appears to have on CV disease risk among women compared with men.[40]

Regarding arterial hypertension, the multivariable analysis showed a non-significant association between systolic blood pressure and APR only in women. Similarly, a recent Norwegian study assessing 3280 healthy people reported an independent and statistically significant association between CRP and higher systolic and diastolic blood pressure only in women.[19] In contrast, in our series the disease activity indices were only associated with blood pressure in men.

Finally, we found an independent association between obesity measured by body mass index and waist circumference and inflammatory activity in both sexes. However, the adjusted OR was generally higher in women, suggesting a stronger relationship in women with axSpA. This finding is consistent with studies conducted both in the general population, which report a stronger association between CRP and obesity in healthy women,[18 41] and in patients with axSpA, where only women show a significant association between body mass index and CRP.[42]

In our study, most of the CV parameters analysed were also associated with BASFI and BASMI, an index of functional and metrological status highly dependent on inflammatory load.

We also observed sex differences in the proatherogenic effect that inflammation can exert independently of traditional CV risk factors. Male patients with elevated CRP at diagnosis showed more carotid plaques at enrolment compared with those with normal basal CRP, regardless of the burden of traditional CV risk factors. In contrast, among women with elevated basal CRP, only those with high–very high SCORE exhibited an increased prevalence of carotid plaques. The reasons why women with low–moderate SCORE showed no relationship between inflammation and atherosclerosis are unknown. Due to their age, most of the women included in this category of risk were premenopausal, while most postmenopausal women were categorised as having a high–very high CV risk. Oestrogen has been hypothesised to have a cardioprotective role mediated by both direct and indirect effects on serum lipids, coagulation, fibrinolytic and antioxidant factors.[43] It could be argued that sex hormones may also play a CV protective role in premenopausal women by ameliorating the proatherogenic effect of inflammation, and consequently, the menopausal transition would imply a more deleterious effect of inflammation on vascular health. This hypothesis could help explain the variation of the relationship between inflammation and atherosclerosis observed across the different SCORE risk groups only among women.

The cross-sectional analysis is a limitation of our study since it cannot determine the nature of the relationship between the inflammatory activity and parameters of CV risk. Data on CV risk factors at the time of diagnosis, included in the retrospective analysis, could constitute another limitation since they were acquired from the medical history. The multicentre 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 minimise variability. The considerably lower proportion of women compared with men could be an additional limitation which would explain that some associations common to both sexes were statistically significant only in men. Further studies with a higher female representation are necessary to clarify this point. Besides, we acknowledge the limitation that, despite being statistically significant, some of the differences between male and female patients had a small size effect.

The present study indicates that inflammation seems to exert a double proatherogenic effect in patients with

axSpA, acting through the classic CV risk factors and independently of them. This relationship shows significant gender differences that, taken together, point to a greater influence of inflammation on CV risk in women. This finding could help explain the greater increase in CV risk that is usually observed in women with inflammatory diseases, although studies in other IMIDs should be performed to confirm this point. Our results highlight the importance of carrying out adequate primary prevention of CV disease in men and women with inflammatory diseases that allow us to keep classic CV factors under control and support the need to achieve strict control of inflammation in our patients.

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