


## ORIGINAL RESEARCH

# Endothelial dysfunction and increased carotid intima-media thickness in patients with spondyloarthritis without traditional cardiovascular risk factors

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**ABSTRACT**

**Background** The aim of our study was to assess subclinical atherosclerosis in spondyloarthritis (SpA) by combining three ultrasound methods (flow-mediated dilation (FMD), carotid intima-media thickness (cIMT) and Ankle Brachial Index (ABI)) and to determine the predictive factors of these parameters.

**Methods** This was a case control study conducted over 12 months including 47 patients with SpA-free-cardiovascular (CV) disease in comparison with age and sex matched 47 healthy controls. Sociodemographic, clinical and biological features as well as therapeutic modalities were recorded in our patients. All subjects had Doppler ultrasound with measurement of cIMT, FMD and ABI. Ultrasound measurements were compared between patients and controls. Linear regression was performed and assessed by machine learning to determine the predictive models of markers of subclinical atherosclerosis.

**Results** We found higher cIMT ( $p < 0.0001$ ), lower FMD ( $p = 0.008$ ) and higher left ABI (0.048) in patients with SpA compared with controls. cIMT was positively correlated to patient-related parameters (age, systolic blood pressure) and disease parameters (age at onset of SpA, disease duration and renal involvement). Biologically, cIMT was positively correlated with creatinine, blood-glucose, total cholesterol (CT) and CT/cholesterol-high density lipoprotein ratio. FMD was negatively correlated with male gender, age, systolic blood pressure, creatinine, blood glucose and Left Lequesne Index. ABI was significantly associated with diastolic blood pressure. Multiple regression analysis identified age, CT and creatinine as independents predictive factors for increased cIMT. Regarding endothelial dysfunction, blood glucose and Left Lequesne Index were the independents predictive factors of decreased FMD.

**Conclusion** Our study supported the accelerated subclinical atherosclerosis in patients with SpA. This subclinical atherosclerosis was mainly mediated by traditional CV risk factors.

**INTRODUCTION**

Spondyloarthritis (SpA) is the second most prevalent chronic rheumatic inflammatory

**WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT?**

- ⇒ Increased cardiovascular (CV) risk in spondyloarthritis (SpA) is mainly due to accelerated atherosclerosis.
- ⇒ The mechanisms and mediators of accelerated atherosclerosis in SpA are not fully elucidated.

**WHAT DOES THIS STUDY ADD?**

- ⇒ This study supported the accelerated subclinical atherosclerosis in young patients with SpA (<50 years old) without known CV risk factors or history of CV disease as showed the significantly increased carotid intima-media thickness and endothelial dysfunction versus controls.
- ⇒ Despite the exclusion of history of CV disease, the predictive factors of markers of subclinical atherosclerosis were traditional CV risk factors (levels of creatinine, total cholesterol and age).

**HOW MIGHT THIS IMPACT ON CLINICAL PRACTICE?**

- ⇒ This highlights the need of tight control of the traditional CV risk factors in patients with SpA, and early assessment of subclinical atherosclerosis even for those without history of CV risk factor.

disease that mainly affects axial skeleton and various extra-articular manifestations. The evidence supporting a premature cardiovascular (CV) risk and an increase in CV morbidity and mortality in this population is in perpetual progress. This increased CV diseases is mainly due to accelerated atherosclerosis in comparison with general population.<sup>1 2</sup> However, this hypothesis remains controversial in other series which have shown the absence of an increase in atherosclerosis markers in patients with SpA compared with controls.<sup>3 4</sup> To date, the mechanisms and mediators of accelerated atherosclerosis in

SpA are not as clear as in rheumatoid arthritis. This would result from a complex interaction between the over-representation of traditional CV risk factors in patients with SpA and the inflammatory burden of the disease.<sup>5</sup>

The effects of subclinical atherosclerotic changes are manifested on the development of endothelial dysfunction, on the arterial wall by an increase of intima-media thickness (IMT) and decreasing vascular elasticity. Assessing these all subclinical stages of atherogenesis is possible through the use of validated non-invasive imaging techniques, which allow early detection of lesions, such as microvascular lesions. Impairment of endothelial function was considered the initial step in the pathogenesis of atherosclerosis. The technique of flow-mediated dilation (FMD) is the most used parameter for assessing endothelial dysfunction.<sup>6</sup> Reduced FMD is directly correlated with endothelium dysfunction and coronary artery disease.<sup>7,8</sup> In this sense, endothelial dysfunction was previously described in a series of patients with psoriatic arthritis, a subtype of SpA, without traditional CV risk factors or previous history of CV events.<sup>9</sup>

Ultrasound (US) measurement of carotid IMT and detection of carotid plaques represent also a non-irradiating, reproducible, rapid and reliable approach.<sup>10</sup> Both carotid IMT and carotid plaques were found to be good predictors of CV events in non-rheumatic individuals. In patients with rheumatoid arthritis, which is the prototype of inflammatory arthritis, endothelial dysfunction, increased carotid IMT and accelerated atherosclerosis are also observed.<sup>11</sup> Furthermore, carotid IMT and carotid plaques were also found to be predictors of CV events and CV death in patients with rheumatoid arthritis.<sup>12,13</sup> The Ankle Brachial Index (ABI) is also a marker of CV risk and a valid method for evaluating arterial stiffness.<sup>10</sup> These US parameters (FMD and carotid IMT) were considered as predictors of distinct CV events in patients with SpA.<sup>14</sup> The usefulness of the evaluation of a single US parameter in CV risk stratification remains debated.

However, there is no study that has evaluated all of these three markers of early atherosclerosis mentioned above, and corresponding to different stages of subclinical atherosclerosis (endothelial dysfunction, increase in IMT, arterial stiffness) in patients with SpA. The aims of our study were to assess subclinical atherosclerosis by combining these 3 US parameters (the FMD, the carotid IMT and the ABI) in patients with SpA compared with healthy controls, and to determine the predictive factors of these parameters.

## METHODS

This was a case control study performed over 12 month's period. We included consecutive patients older than 18 years, who met the definitions of axial or peripheral SpA according to the Assessment of Spondyloarthritis International Society (ASAS) criteria.<sup>15,16</sup> The controls were healthy volunteers recruited from the paramedical staff

or patients consulting for degenerative joint diseases. Healthy controls were matched with the patients according to age, sex and body mass index (BMI). Subjects (patients and controls) were not included if they presented a previous history of CV disease (ischaemic heart disease, cerebrovascular accident, peripheral arterial disease or heart failure); or at least one CV risk factor reported by patient and diagnosed for more than 3 months among the following (age > 50 years, high blood pressure, diabetes mellitus, dyslipidaemia, chronic renal failure, smoking, alcoholism, hyperuricaemia, gout, total obesity defined by a BMI > 30 kg/m<sup>2</sup>). Patients with SpA associated to psoriasis, inflammatory bowel diseases, juvenile SpA or reactive arthritis were also not included. This study had obtained the local hospital ethical committee approval. According to the Declaration of Helsinki of the World Medical Association, all patients were informed beforehand of the objective of the study and consented to the use of their clinical and paraclinical data.

For each patient, the sociodemographic data including (age, gender, marital status, education level and occupation) were recorded. Anthropometric measures were mentioned (weight, height, waist circumference, hip circumference) for cases and healthy controls. Disease characteristics were collected (age at onset of SpA, age at diagnosis, disease duration, phenotypic presentation of SpA, extra articular manifestations). Patient-reported outcomes (PRO) were measured (duration of morning stiffness, patient global assessment, evaluation of axial and peripheral pain using Visual Analog Scale). The following scores were calculated: the Bath Ankylosing Spondylitis Global Score (BAS-G), the metrologic index (Bath Ankylosing Spondylitis Metrology Index, BASMI) and the enthesitis index (Maastricht Ankylosing Spondylitis Enthesitis Score, MASES).

Inflammatory parameters for assessment of disease activity were the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), the Ankylosing Spondylitis Disease Activity Score (ASDAS), and C reactive protein (CRP). For peripheral SpA, we evaluated the number of tender joints and number of swollen joints. Functional status was assessed by Bath Ankylosing Spondylitis Functional Index (BASFI). Lequesne algofunctional Index was obtained for patients with established hip involvement.

## Biological data

Blood count, fasting blood glucose, creatinine and lipids (total cholesterol (CT), triglycerides (TG), high density lipoprotein-cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), CT/HDL-C and LDL-C/HDL-C ratios) were measured from venous blood samples after a 12-hour fast in all patients and controls at the time of enrolment.

## Therapeutic data

Non-steroidal anti-inflammatory drugs (NSAIDs), conventional disease-modifying antirheumatic drugs (csDMARDs) and tumour necrosis factor (TNF)- $\alpha$

inhibitors were recorded for each patient. Dose, frequency and duration of NSAIDs treatment were quantified by the ASAS NSAIDs index.<sup>17</sup>

### US assessment

High-resolution Doppler ultrasonography was performed with a Mindray Resona 7 ZST+ and a 11-MHz linear array transducer. The subjects were placed in a quiet air-conditioned room with a temperature around 24°C. Vasoactive drugs, intense physical exercise and consumption of caffeinated substances or foods rich in vitamin C or fat, were stopped 24 hours before US examination.<sup>18</sup> The US measurements were performed by the same radiologist, for all subjects after at least 6 hours of fasting and 15 min of rest, in supine position.

### Carotid intima media thickness

The probe was set longitudinally to keep the acoustic beam vertical with the anterior and the posterior wall of the common carotid artery (CCA) and so parallel to the screen. IMT was measured on the posterior (far) wall as the distance from the leading edge of the first echogenic line to the leading edge of the second echogenic line, as described previously. It was measured in the wall of the most distal 20 mm length of the CCA, just proximal to the bifurcation. Carotid IMT and the average IMT were determined using automatic software called real-time IMT which can monitor and calculate the thickness of the carotid intima automatically. Three measurements of IMT were taken for the far wall of both the right and left common CCA. The IMT was determined as the average of three measurements in each CCA. Left, right and mean carotid IMT values were considered. We considered that abnormal carotid IMT > 0.7 mm, IMT > 1.5 mm reflected carotid plaque and IMT < 0.7 mm was normal.<sup>19</sup>

### Flow-mediated dilation

US examination was performed on the right arm. B-mode longitudinal section was obtained of the brachial artery above the antecubital fossa: a segment with clear anterior and posterior intimal interfaces between the lumen and vessel wall was selected for continuous 2D grayscale imaging. A sphygmomanometer cuff was placed on the forearm distal to the brachial artery and the transducer position is fixed. After the baseline determination of the end-diastolic diameter, reactive hyperaemia was induced by release of a pneumatic cuff around the forearm inflated to supra-systolic pressure for 5 min. After deflation, the arterial diameter was recorded. Relative FMD (FMD%) was calculated as the percentage change from baseline to the maximum diameter of the artery.<sup>20</sup> The percentage of FMD reflects endothelial function. The lower FMD's percentage indicated the impairment of vascular dilation after deflation of the cuff was reduced. Thus, the lower the FMD's percentage, the higher the likelihood of endothelial dysfunction. As the FMD cut-off value therefore has not yet been standardised, this

measure was considered as being a binary continuous variable without limit value.<sup>10</sup>

### Ankle Brachial Index

After 15 min of rest in the supine position, systolic blood pressures (SBP) of brachial arteries, posterior tibial arteries and anterior tibial arteries in both arms and ankles were measured. We have used a continuous-wave Doppler probe for detection of arterial flow. The SBP was determined with a pneumatic cuff, which is first inflated until flow ceases and then deflated slowly until there was reappearance of the flow signal. The corresponding cuff pressure was the SBP. To calculate the right ABI, we considered the highest value of the right anterior tibial artery SBP and the right posterior tibial artery SBP measurements, and then this value was divided by the brachial homolateral artery SBP. Left ABI was calculated in the same way. An ABI > 1.3 (arterial incompressibility) is a predictive factor of an increased CV risk; ABI < 0.9 provides information on the existence of obliterating arteriopathy of the lower limbs; and ABI value was normal between 0.9 and 1.3.<sup>21</sup>

### Reproducibility assessment

In order to verify interobserver reproducibility, US assessments were performed in double blind by the radiologist investigator and an expert angiologist with 8 years of experience for three patients, on three successive US measurements.

The evaluation of intraobserver reproducibility was studied by the same operator (radiologist) for three patients at two times (at the start of the study and at the end of the study), taking all the 3 US parameters.

-Kappa concordance coefficient (k) was used to calculate interobserver and intraobserver reproducibility. The pathological threshold of carotid IMT was set at 0.7 mm, of the ABI were set at 0.9 and 1.3. As there is no pathological limit value for FMD. Just for calculating reproductibility, the threshold was set arbitrarily using a Tunisian population as a reference, having set this threshold at 10%.<sup>7</sup> These k intervals and thresholds were used to measure intraobserver and interobserver agreement: discordance (<0.0), bad (0.0–0.20), poor (0.21–0.40), moderate (0.41–0.60), good (0.61–0.80), excellent (>0.81).

### Statistical analysis

Statistical analysis was performed using SPSS V.25 (IBM Corp.) and Python for graphs, tables and calculations. Python software is a computer programming technique used in the field of Machine Learning and Data Science allowing simple prototyping, flexible analysis of numerical algorithms and rapid data mining.

The quantitative variables were expressed as median and IQR between the 25th and 75th percentiles (IQR). The qualitative variables were summarised as percentages. For data analysis, given the size of the sample and the non-normality of the distribution of the variables,



we used the following non-parametric tests: the Mann-Whitney U test for comparing medians between two quantitative variables, the Pearson's  $\chi^2$  test for studying the association between two independent qualitative variables, the Kruskal-Wallis H for the comparison of medians between more than three quantitative variables.

The Cramer's Phi and V test were used to identify the strength of the association. The 'input' method was used for the multivariate study with a 95% CI and the Durbin-Watson residual study. The significance level was set at 0.05.

Linear regression was performed for potential confounding factors and assessed by machine learning to predict IMT, FMD and ABI. Variables with good correlation and good linearity were selected for machine learning. Four predictive models were used from the 'Scikit-learn' framework: multiple linear regression, Ridge linear regression, Lasso linear regression and polynomial regression. For each predictive model, mean absolute error (MAE), mean square error (MSE), root mean square error (RMSE) and R-squared score ( $R^2$ ) were calculated to evaluate predictive models. A predictive model was selected when the  $R^2$  is high and the value of MAE, MSE and RMSE is low.

## RESULTS

Among the 352 patients with SpA recruited in our rheumatology department, after application of selection criteria, 47 SpA were eligible (the flowchart summarised the process of inclusion of patients is available in online supplemental file 1). A total of 94 participants, of which 47 were volunteer controls and 47 were patients with SpA, were examined. The controls were age, sex and BMI matched with the patients (table 1).

### Demographic, disease characteristics and laboratory data

Median (IQR) age of patients was 36 (26–46) years; sex ratio was 2.35. The main features of SpA group were summarised in table 2. Regarding disease-related data, the median (IQR) age at onset of SpA was 20 (18–32)

years; the median (IQR) disease duration was 11 (5–16) years. Median (IQR) scores were for BASMI 1.5 (0–4); MASES 0 (0–0); BASFI 3 (1.5–5.1), BASDAI 2.6 (1.8–3.8) and ASDAS-CRP 2.18 (1.62–2.91). BASDAI >4 was noted in 21%; and ASDAS-CRP >2.1 in 55% of patients. According to Lequesne Index, the severity of the hip handicap was considered severe to extremely severe in 7 cases on the right hip, and in 11 cases on the left hip.

At the time of study, median (IQR) serum levels of CRP and CT were 6.45 (1.5–19.9) mg/L and 3.66 (3.18–4.28) mmol/L, respectively (table 3). High serum levels of these parameters: CRP, CT and TG were noted in 45%, 4% and 6% of patients, respectively. Higher Atherogenicity Index was found in 17% of patients for CT/HDL-C ratio and 9.3% for LDL-C/HDL-C ratio. NSAIDs were used continuously in 19 patients. The median (IQR) ASAS NSAIDs score was 20 (0–70).

The comparison of patients to controls in terms of conventional CV risk factors (blood pressure, glucose, creatinine and lipid parameters) did not show significant difference (tables 1 and 3).

### Reproducibility

The assessment of the interobserver reproducibility of the 3 US measurements (IMT, FMD, ABI) concluded that there were: excellent agreement for IMT ( $k=0.824$ ;  $p=0.015$ ), good agreement for ABI ( $k=0.742$ ;  $p=0.036$ ) and good agreement for FMD ( $k=0.696$ ;  $p=0.048$ ). The assessment of intraobserver reproducibility demonstrated: excellent agreement for IMT ( $k=0.851$ ;  $p=0.011$ ), excellent agreement for ABI ( $k=0.824$ ;  $p=0.025$ ) and good agreement for FMD ( $k=0.752$ ;  $p=0.038$ ).

### US assessment

Median IMT of the right, the left CCA as well as their means were significantly increased in patients than matched controls. Table 4 shows the distribution of the US parameters between the patients with SpA and the

**Table 1** Comparison between patients and controls (clinical data)

	Patients SpA	Controls	P value
Age (years), median (IQR)	36 (28–46)	32 (26–43)	0.267
Gender (M%)	70.2%	70.2%	0.589
Weight (kg), median (IQR)	69 (56–80)	80 (65–83)	<b>0.021*</b>
Height (m), median (IQR)	1.70 (1.63–1.75)	1.72 (1.67–1.8)	0.054
BMI (kg/m <sup>2</sup> ), median (IQR)	24.49 (20.72–26.87)	24.91 (22.99–27.17)	0.238
Waist circumference (cm), median (IQR)	88 (82–97)	79 (72–88)	<b>&lt;0.0001*</b>
Hip circumference (cm), median (IQR)	100 (91–109)	99 (87–107)	0.396
SBP (mm Hg)	121 (110–130)	126 (98–132)	0.289
DBP (mm Hg)	71 (67–78)	68 (61–76)	0.323

\*  $p<0.05$   
 BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure; SpA, spondyloarthritis.

**Table 2** Demographics, disease characteristics, laboratory and therapeutic data in patients with spondyloarthritis (SpA)

	Median (IQR 25%–75%)	Min	Max
Age (years)	36 (28–46)	18	50
Sex ratio	2.35		
Marital status (%)			
Unmarried	55		
Married	41		
Divorced	4		
Educational attainment (%)			
Primary education	17		
Secondary education	64		
University	19		
Profession (%)			
Unemployed	17		
Student	11		
Employed	72		
Age of onset of SpA (years)	20 (18–32)	16	43
Age at diagnostic (years)	28 (22–35)	16	46
Disease duration (years)	11 (5–16)	1	32
Type of SpA (%)			
Axial	58		
Axial and peripheral	40		
Peripheral	2		
Extra-articular manifestation			
Uveitis	9		
Nephropathy	4		
Osteoporosis	6		
BASMI	1.5 (0–4)	0	7
PRO			
Morning stiffness (min)	5 (0–15)	0	180
PGA	4 (3–6)	0	9
VAS axial pain	5 (3–6)	0	9
VAS peripheral pain	0 (0–0)	0	7
BAS-G	50 (30–60)	10	90
MASES	0 (0–0)	0	4
Number of tender joints	0 (0–0)	0	4
Number of swollen joints	0 (0–0)	0	0
BASDAI	2,6 (1,8–3,8)	0,2	6,5
ASDAS-CRP	2,18 (1,62–2,9)	0,32	4,3
BASFI	3 (1,5–5,1)	0,6	8,7
Lequesne AFI of the right hip	7 (5–8)	4	16
Lequesne AFI of the left hip	8 (5–10)	4	21
NSAIDs, %	91		

Continued

**Table 2** Continued

	Median (IQR 25%–75%)	Min	Max
csDMARDs, %	41		
TNF inhibitors, %	38		

AFI, Algo-Functional Index; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BAS-G, Bath Ankylosing Spondylitis Global Score; BASMI, Bath Ankylosing Spondylitis Metrology Index; CRP, C reactive protein; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; Max, maximum; Min, minimum; NSAIDs, non-steroidal anti-inflammatory drugs; PGA, patient global assessment; PRO, patient-reported outcomes; TNF, tumour necrosis factor; VAS, Visual Analogue Scale.

healthy controls after adjusting for the conventional CV risk factors. A pathological IMT value >0.7 mm was noted in 8 patients according to the following distribution: right CCA (n=2), left CCA (n=7), the average measurement of the IMT (n=3). No atherosclerotic plaque (IMT>1.5 mm) was found. Median FMD was lower in patients with SpA compared with controls with a statistically significant difference (p=0.008). Left ABI was significantly higher in patients with SpA compared with controls (p=0.048). No statistically significant difference was observed between patients with SpA and controls regarding right ABI and mean ABI (table 4). Normal values of ABI between (0.9–1.3) were found in 34 patients with SpA versus 44 controls, ABI between (0.7–0.9) (2 patients) and ABI>1.3 were noted in 11 patients with SpA versus 3 healthy controls.

### Correlation analysis

We considered for correlation analysis, the average value of carotid IMT and ABI (table 5).

Age was positively correlated with carotid IMT and negatively correlated with FMD. The analysis by age group of the 3 US parameters showed a statistically significant difference in the IMT between the subjects belonging to different age groups (p=0.004). Median carotid IMT increased significantly with the age. Median FMD was significantly lower in male gender (p=0.036) and married patients (p=0.013). Moreover, the median IMT varied significantly in terms of the different professional occupations (p=0.036). Unemployed patients had the highest IMT. SBP was positively correlated with carotid IMT (p<0.0001; r=0.513), and negatively correlated with FMD (p=0.045; r=-0.297). However, diastolic blood pressure was positively correlated with ABI (p=0.019; r=0.345).

Concerning disease characteristics, both age of onset of SpA and disease duration were positively correlated with carotid IMT (table 5). Renal involvement was also significantly associated with IMT (p=0.045). The other systemic manifestations were not associated with US measurements. By univariate regression analysis, none of the disease activity scores (BASDAI, ASDAS-CRP), the PRO

**Table 3** Laboratory data

Variable, median (IQR)	Patients with SpA	Controls	P value
CRP (mg/L)	6.45 (1.5–19.9)	4.1 (1.45–7.25)	0.001
Fasting blood sugar (mmo/L)	4.93 (4.55–5.1)	4.88 (4.51–5.08)	0.639
Creatinine (µmol/L)	63 (58.5–74)	63 (55–70)	0.342
Total cholesterol (mmo/L)	3.66 (3.18–4.28)	3.60 (3.46–4.23)	0.904
Triglycerides (mmo/L)	0.84 (0.79–1.15)	0.92 (0.78–1.06)	0.946
C-LDL (mmo/L)	2.17 (1.78–2.6)	2.1 (1.7–2.5)	0.943
C-HDL (mmo/L)	1.08 (0.92–1.2)	1.16 (0.99–1.31)	0.052
CT/C-HDL	3.48 (2.95–3.97)	3.21 (2.69–3.77)	0.248
C-LDL/C-HDL	1.99 (1.54–2.48)	1.9 (1.43–2.31)	0.339

CRP, C reactive protein; CT, total cholesterol; HDL-C, high density lipoprotein cholesterol ; LDL-C, low density lipoprotein cholesterol.

and the disease index (BAS-G, MASES, BASMI, BASFI) were associated with any of the US vascular measurements. However, there was a significant and strongly negative correlation with strong linearity between the Lequesne Index of the left hip and FMD ( $p < 0.0001$ ;  $r = -0.846$ ).

As regards biological parameters, we found a positive correlation between carotid IMT and the values of fasting blood sugar ( $p = 0.009$ ), creatinine: ( $p = 0.002$ ), CT ( $p = 0.007$ ) and CT/C-HDL ratio ( $p = 0.028$ ). While a positive correlation was also found between FMD and platelets count ( $p = 0.027$ ), a negative correlation was obtained between FMD and the values of fasting blood sugar ( $p = 0.012$ ) and creatinine: ( $p = 0.001$ ).

There was no significant association between the ASAS-NSAIDs index score and the various US parameters: IMT, FMD and ABI ( $p = 0.390$ ,  $p = 0.285$ ,  $p = 0.126$ ; respectively). The univariate study did not show any significant association between the various other treatments (csDMARDs, TNF inhibitors) and the US parameters.

The analysis of the association between these 3 US measurements revealed that FMD was the only measure negatively correlated with carotid IMT of the left CCA ( $p = 0.027$ ;  $r = -0.322$ ) and left ABI ( $p = 0.042$ ;  $r = -0.297$ ). The results of the correlation analysis for carotid IMT, FMD and ABI are shown in [table 6](#).

### Predictive model to establish patients with SpA with high CV risk

There was no multivariate study for ABI because the associations were not significant.

The best prediction was given by machine learning (the multiple linear regression model). The  $R^2$  score was the highest ( $R^2 = 0.535$ ). MAE=0.05, RMSE=0.069 and MSE=0.004 were the lowest in this model. This model suggested that 53.52% of the patients with SpA with higher CV risk according to carotid IMT would be detected by the combination of the following variables: age, creatinine and CT ( $R^2 = 0.535$ ). The independent risk factors of carotid IMT were age, creatinine and CT.

As for FMD, the model obtained provided a good prediction ( $F = 28.962$ ,  $p < 0.0001$ ). The data fit the model well ( $R = 0.897$ ). The independence of errors was respected (Durbin Watson test=2.462). The model suggested that 80.5% of FMD could be predicted by the combination of Left Lequesne Index and blood sugar ( $R^2 = 0.805$ ) ([table 7](#)). The independent risk factors of FMD were Lequesne Index of the left hip and blood sugar.

### DISCUSSION

The present study confirmed the accelerated subclinical atherosclerosis in patients with SpA compared with

**Table 4** Comparison of ultrasound parameters between patients with spondyloarthritis (SpA) and healthy controls

	SpA	Controls	P value
IMT right CCA (mm)**	0.54 (0.50–0.63)	0.45 (0.42–0.50)	<0.0001
IMT left CCA (mm)**	0.55 (0.49–0.61)	0.47 (0.45–0.50)	<0.0001
IMT mean (mm)**	0.55 (0.48–0.62)	0.46 (0.43–0.50)	<0.0001
FMD (%)	14.6 (9–24)	18.18 (12.8–23.1)	0.008
Right ABI**	1.15 (1.00–1.25)	1.16 (1.07–1.2)	0.988
Left ABI**	1.20 (1.08–1.3)	1.15 (1.07–1.23)	0.048
Mean ABI**	1.18 (1.05–1.29)	1.18 (1.05–1.21)	0.213

\*Data represent median (IQR).  
ABI, Ankle Brachial Index; CCA, common carotid artery; FMD, flow-mediated dilation; IMT, intima media thickness.

**Table 5** Correlations between ultrasound measurements, patient-related parameters and disease characteristics

	IMT (mm)			ABI			FMD (%)		
	P value	r	R <sup>2</sup>	P value	r	R <sup>2</sup>	P value	r	R <sup>2</sup>
Age (years)	<b>&lt;0.0001</b>	<b>0.578</b>	<b>0.334</b>	0.911	0.017	NS	<b>0.017</b>	<b>-0.347</b>	<b>0.120</b>
BMI	0.310	0.151	NS	0.630	-0.072	NS	0.437	-0.116	NS
Age at onset of SpA	<b>0.002</b>	<b>0.440</b>	<b>0.194</b>	0.832	-0.032	NS	0.083	-0.258	NS
Disease duration	<b>0.05</b>	0.287	0.082	0.618	0.075	NS	0.172	-0.203	NS
SBP (mm Hg)	<b>&lt;0.0001</b>	0.513	0.263	0.413	0.124	NS	<b>0.045</b>	-0.297	0.088
DBP (mm Hg)	0.055	0.285	NS	<b>0.019</b>	0.345	0.119	0.138	-0.222	NS
NSJ	0.925	0.014	NS	0.099	0.243	NS	0.445	-0.114	NS
NTJ	0.426	0.119	NS	0.803	0.037	NS	0.173	0.202	NS
BAS-G	0.741	-0.050	NS	0.972	-0.005	NS	0.463	0.110	NS
MASES	0.232	-0.178	NS	0.136	0.221	NS	0.855	-0.027	NS
BASDAI	0.971	0.005	NS	0.715	0.055	NS	0.097	0.245	NS
ASDAS-CRP	0.600	-0.079	NS	0.982	-0.003	NS	0.199	0.193	NS
BASMI	0.552	0.09	NS	0.256	-0.171	NS	0.401	0.127	NS
BASFI	0.292	0.157	NS	0.342	-0.146	NS	0.573	-0.084	NS
AFI right Lequesne	0.136	-0.337	NS	0.852	-0.043	NS	0.391	-0.198	NS
AFI left Lequesne	0.528	-0.159	NS	0.148	-0.356	NS	<b>&lt;0.0001</b>	<b>-0.846</b>	<b>0.716</b>
Hgb	0.908	0.017	NS	0.752	0.047	NS	0.086	-0.253	NS
WBC	0.617	0.075	NS	0.405	-0.124	NS	0.416	0.122	NS
PLT	0.183	-0.198	NS	0.136	-0.221	NS	<b>0.027</b>	<b>0.322</b>	0.104
CRP	0.569	-0.086	NS	0.136	-0.223	NS	0.374	0.134	NS
Creatinine	<b>0.002</b>	<b>0.445</b>	0.198	0.077	0.266	NS	<b>0.001</b>	<b>-0.490</b>	0.240
Blood glucose	<b>0.009</b>	<b>0.387</b>	0.150	0.406	0.128	NS	<b>0.012</b>	<b>-0.375</b>	0.140
CT	<b>0.007</b>	<b>0.404</b>	0.163	0.232	-0.186	NS	0.457	-0.116	NS
TG	0.093	0.259	NS	0.822	-0.035	NS	0.374	-0.139	NS
LDL-C	0.073	0.276	NS	0.147	-0.225	NS	0.239	-0.184	NS
HDL-C	0.875	-0.025	NS	0.622	0.077	NS	0.343	-0.148	NS
CT/HDL-C	<b>0.028</b>	<b>0.340</b>	0.116	0.275	-0.173	NS	0.767	-0.047	NS
LDL-C/HDL-C	0.121	0.240	NS	0.151	-0.223	NS	0.663	-0.068	NS

ABI, Ankle Brachial Index ; AFI, Algo Functional Index; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functionnal Index; BAS-G, Bath Ankylosing Spondylitis Global Score; BASMI, Bath Ankylosing Spondylitis Metrology Index; BMI, body mass index; CRP, C reactive protein; CT, total cholesterol; DBP, diastolic blood pressure; FMD, flow-mediated dilation; HDL-C, high density lipoprotein cholesterol; Hgb, haemoglobin; IMT, intima media thickness; LDL-C, low density lipoprotein cholesterol; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; NS, not significant; NSJ, number of swollen joints; NTJ, number of tender joints; p, significance coefficient; PLT, platelets; R<sup>2</sup>, linearity; r, association; SBP, systolic blood pressure; SpA, spondyloarthritis; TG, triglycerides; WBC, white blood cells.

**Table 6** Correlation between FMD and IMT, ABI

	P value	R	R <sup>2</sup>
Left IMT/FMD	<b>0.027</b>	<b>-0.322</b>	0.104
Left ABI/FMD	<b>0.042</b>	-0.297	0.089

ABI, Ankle Brachial Index ; FMD, flow-mediated dilation; IMT, intima media thickness; p, significance coefficient; r, association; R<sup>2</sup>, linearity.

healthy controls. Compared with matched volunteers, carotid IMT was significantly increased in patients with SpA, and FMD was significantly lower in patients with SpA. Multivariate regression analysis identified independents predictive factors for increased carotid IMT which were age, creatinine and CT; and the independents predictive factors for decreased FMD were fasting blood sugar levels and Lequesnealgofunctional Index of the left hip. Thus, through the analysis of predictive models, this increased CV risk was almost exclusively explained by conventional



**Table 7** FMD predictive factors

	B	P value	95% CI	
			Low	Up
Constant	24 455	0.012	6178	42 732
Left Lequesne AFI	-1.207	<b>&lt;0.0001</b>	-1.568	-0.845
Blood glucose	-4.746	<b>0.015</b>	-8.437	-1.055

AFI, Algo-Functional Index ; B, equation's coefficient ; p, significance coefficient; t, contribution coefficient.

CV risk factors rather than disease-specific features or measures of inflammation (BASDAI, ASDAS, CRP).

The choice of these 3 US measurements was motivated by the fact that they are simple, economical techniques and therefore reproducible in common practice. Moreover, each measure assessed a pathophysiological mechanism of atherosclerosis at different stages and therefore an optimal appreciation of the vascular state in patients with SpA. IMT informed about wall infiltration, FMD is the marker of endothelial function while ABI is the marker of arterial stiffness.

Concerning results of carotid IMT, our results are in concordance with several previous studies who observed a significantly increased carotid IMT in patients with SpA compared with controls.<sup>1 2 22-25</sup>

Our study confirmed endothelial dysfunction in patients with SpA, as has been demonstrated in some reports.<sup>2 26 27</sup> A few studies have investigated FMD in SpA, but they all demonstrated a significant decrease in FMD in patients with SpA compared with healthy subjects. In addition, Bodnár *et al* found a negative correlation between FMD and the IMT.<sup>27</sup> This was consistent with our results. In our series, we found a significant negative correlation between FMD and left IMT.

In order to determine the mechanism of endothelial dysfunction in SpA, some authors have conducted studies on vascular endothelial biomarkers. Verma *et al* found significantly lower serum levels of endothelial progenitor cells, a serum marker of vascular endothelium repair, in patients with SpA compared with healthy controls showing impaired endothelial function in SpA.<sup>28</sup> Asymmetric dimethylarginine, an endogenous NO inhibitor and marker of endothelial function, was significantly increased in the serum of patients with SpA.<sup>29 30</sup> Wang and Wang demonstrated that serum vaspin levels were significantly decreased and strongly associated with impaired endothelial function, measured by FMD in patients with SpA.<sup>31</sup> In a large series of patients (n=510 patients), vaspin was found to be associated with CV risk factors that may influence the atherosclerotic process in SpA. Serum vaspin concentration was also found to be genetically modulated in patients with axial SpA.<sup>32</sup> Patients with axial SpA showed higher levels of osteoprotegerin but lower levels of sclerostin than controls.<sup>33</sup> Furthermore, in these patients, calprotectin was associated with adverse lipid profiles and inflammatory biomarkers, which may

further influence the development of atherosclerosis.<sup>34</sup> Finally, serum omentin and mRNA levels were lower in axial patients with SpA compared with controls. Low serum omentin levels were associated with male gender, obesity, inflammatory bowel disease and high Atherogenic Index.<sup>35</sup>

In our study, we did not find any significant difference in mean ABI and between patients and controls. Further analysis of the ABI distribution focusing on the ABI>1.3 subgroup, which represents a marker of CV risk, we found that six patients had ABI>1.3 against a single control. This elevation in ABI values reflects a trend towards arterial incompressibility more evident in patients with SpA than in the general population. An ABI>1.3 indicates arterial incompressibility or arterial stiffness by mediocalcosis mechanism and is associated with increased CV mortality.<sup>36</sup> To our knowledge, this is the first description of tendency towards peripheral arterial incompressibility is SpA. Focusing on the second category of ABI <0.9, we objectified that 4% of patients with SpA versus 0% of healthy controls presented asymptomatic peripheral arterial disease of the lower limbs. Thus, patients with SpA without CV risk factor are exposed to the risk of peripheral arterial disease of the lower limbs. Billim *et al* evaluated the ABI in psoriatic arthritis<sup>37</sup>; they found a significant decrease in right, left and mean ABI compared with healthy subjects.

In our study, age was the strong predictive factor associated with increased carotid IMT, and was negatively correlated with FMD. This finding was in agreement with various studies that had confirmed the positive correlation between age and IMT<sup>3 23 28 38 39</sup> and the negative correlation with FMD.<sup>8 40</sup> Interestingly, we have demonstrated that age was a predictive factor of increased IMT although they were mainly young patients (median age at 36 years and a predominant age group between 30 and 39 years) with an age limit at 50 years old.

Among the disease-related parameters, the Left Lequesne Index was the strongest independent predictor factor of decrease in FMD. To our knowledge, this is the first time to show a positive association between functional impact of coxitis and markers of subclinical atherosclerosis. Median Lequesne Index of the right and left hip was 7 (5–8) and 8 (5–10), respectively; with extremes varying from 4 to 16 for the right hip and 21 for the left hip. Hip functional impairment according to the Lequesnealgorithms Index was considered severe to extremely severe in 7 cases on the right hip, and in 11 cases on the left hip; suggesting severe coxitis on the left hip with more functional impairment. In a study carried out by Mendonça *et al* including 22 patients with SpA, the US resistance index was decreased in the sacral and internal iliac arteries.<sup>41</sup> This decreased artery led to micro and macrovascular changes influencing endothelial function. The decreased resistance index was also correlated with serum markers of inflammation. This hypothesis suggests that the inflammatory process during



coxitis might decrease femoral and internal arteries resistance and thus contribute to endothelial dysfunction.

Some authors have demonstrated that carotid IMT was significantly increased in patients with high disease activity or high CRP.<sup>1 3 4 38 42</sup> Verma *et al* have found a significant correlation between CRP and FMD.<sup>28</sup> In our study, the US measurements were not associated with inflammatory parameters (CRP, disease activity scores). This is in agreement with the majority of results in the literature which showed that inflammatory components do not appear to be the determinants factors of subclinical atherosclerosis.<sup>12 22 23 25 41–46</sup> These authors explained these data by the low levels of CRP and low to moderate disease activity, as in our patients whose median CRP at 6.45 mg/L. The small sample size of our patients may also not allow to detect contributions from measures of disease activity and inflammation. On the other hand, disease activity scores and CRP informed more on acute inflammatory status at the time of assessment. However, in SpA, spinal radiographic progression reflects rather the effects of long-term and cumulative inflammation.<sup>47 48</sup>

Giollo *et al* were the first authors who had shown that renal function was an independent predictor of accelerated atherosclerosis in patients with SpA.<sup>46</sup> This is consistent with our results. Indeed, although all patients with SpA included in this work have normal renal function, creatinine level was an independent risk factor of increased carotid IMT, and renal involvement was significantly associated with IMT. We have also found that renal function was correlated to endothelial dysfunction. The Ambulatory Arterial Stiffness Index has been recently demonstrated as an independent risk factor for accelerated age-related glomerular filtration rate decline in the general middle-aged population.<sup>49</sup> Blood sugar was an independent predictor of endothelial dysfunction, and positively correlated with carotid IMT. We emphasise the importance of this result; this highly significant correlation with two markers of subclinical atherosclerosis was observed in young patients aged less than 50 years old, non-diabetics and having normal fasting blood sugar except one patient whose level was at the upper limit of normal. To our knowledge, this is the first study that had shown that blood sugar was an independent predictor of accelerated atherosclerosis in patients with non-diabetic SpA. Thus, blood sugar monitoring is essential since it is correlated with US measurements in these patients who are free of CV risk factor.

Regards lipid profile, CT was identified as an independent predictor of accelerated atherosclerosis. Interestingly and similarly, our study population comprised patients with no history of dyslipidaemia and lipid profile was near to the range of normality (only 2 patients among the 47 included had hypercholesterolaemia). Rueda-Gotor *et al* identified LDL-C as the factors determining reclassification patients with SpA from moderate to high CV risk category after US assessment of carotid IMT and *atherosclerotic* plaques.<sup>23</sup> In consistent with literature

results, we did not find association between endothelial function, arterial stiffness and lipid profile.<sup>26 28 50</sup>

Our study has confirmed that young patients with SpA (<50 years old) without CV risk factors, with low disease activity, have an accelerated subclinical atherosclerosis than general population. US measurements of FMD, carotid IMT and ABI are markers of CV risk with good reproducibility that can be used in CV risk monitoring in patients with SpA. However, we are aware that it is not accessible to carry out systematic US CV screening in all patients with SpA. For this reason, we designed predictive models that identify patients with higher CV burden. Independent predictive factors of increased carotid IMT were age, CT and creatinine. For FMD, the predictive factors of endothelial dysfunction were blood sugar and the Lequesnealgofunctional Index. Thus, we note that the models that predict subclinical atherosclerosis are not disease-related parameters, nor SpA activity, but rather are traditional CV risk factors, and they were able to identify more than 53% of patients with SpA with high CV risk. Conventional CV risk factors appear to be the major contributors to the higher carotid IMT and lower FMD in our SpA sample. The association between conventional CV risk factors and subclinical atherosclerosis in SpA could be linked through adipokines, which take part in both metabolic syndrome<sup>51</sup> and accelerated atherosclerosis in SpA.<sup>32 35 52</sup> The role of adipokines, metabolic syndrome-related biomarkers and biomarkers of endothelial cell activation and inflammation was shown to be relevant in both SpA. Thus, without conventional CV risk factor, chronic inflammatory pathways in SpA may contribute to accelerating the different stages of atherosclerosis. This is in line with the literature as discussed above, and highlights the importance of the global patient care. Non-active SpA may present an increased CV risk in the presence of disrupted and unaddressed traditional CV risk factors.

However, this work has some limitations to consider: the absence of standardised threshold values for the measurement of FMD. To compensate this deficit, it would be more relevant to determine our population own threshold values; the median age of SpA was 11 years with extremes of 1 year and 32 years, this makes the population heterogeneous and could influence the stage of atherosclerosis in these patients; the radiologist performing the US studies was not blinded to diagnosis of SpA. Finally, the differences between ABI measures which left ABI was higher in patients with SpA compared with controls but not mean or right ABI are also a bias for interpretation. These differences may be also related to the exploratory nature of the study and further studies are needed in larger groups to confirm the decreased ABI in SpA.

## CONCLUSION

Our study showed accelerated subclinical atherosclerosis and endothelial dysfunction in a group of patients

with SpA without known CV risk factors compared with matched healthy controls. But within that group conventional CV risk factors (levels of creatinine, CT, age) were the predictive factors of markers of subclinical atherosclerosis. We also noted an increased tendency towards arterial incompressibility. The 3 US measurements characterise different stages of the atherosclerosis process in SpA, structural changes in vessels and arterial stiffness may require more time to be detected than others. These results are consistent with the pre-existing literature, but our data provide novel insight. Indeed, to our knowledge, this is the first study to have shown a link between Lequesnealgofunctional Index and endothelial dysfunction.

These findings highlight the need of both tight control of the traditional CV risk factors in patients with SpA, and early assessment of subclinical atherosclerosis even for those without history of CV risk factor.

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