Predictive factors of increased Epicardial Adipose Tissue Thickness in patients with Spondyloarthritis

Facteurs prédictifs d'augmentation de l'épaisseur du tissu adipeux épicardique chez les patients atteints de spondylarthrite ankylosante

Aicha Ben Tekaya[1,4], Takwa Mehmli[1,4], Imtinene Ben Mrad[2,4], Olfa Saidane[1,4], Leila Rouached[1,4], Selma Bouden[1,4], Rawdha Tekaya[1,4], Ahmed Fendri[3,4], Ines Mahmoud[1,4], Mariem Drissa[5], Leila Abdelmoula[1,4]

Rheumatology Department, Charles Nicolle Hospital, Tunis, Tunisia

Cardiology Department, Habib Thameur Hospital, Tunis, Tunisia

Radiology Department, La Rabta Hospital, Tunis, Tunisia

Faculty of medicine of Tunis, University Tunis El Manar, Tunis, Tunisia

Cardiology Department La Rabta, Tunis, Tunisia

Summary

There is a growing interest in the role of epicardial adipose tissue (EAT) as a novel marker of subclinical coronary atherosclerosis. We aimed to identify the predictive factors of increased EAT thickness in spondyloarthritis (SpA) patients free of cardiovascular risk factors.

We conducted a cross-sectional study including SpA patients and age and gender-matched healthy volunteers without traditional cardiovascular risk factors. General and biological data were obtained for all participants. Disease characteristics and therapeutic modalities were recorded at the time of inclusion. Both patients and control groups underwent echocardiography with measurement of EAT thickness.

A total of 47 SpA patients and 47 healthy controls were included, with a median age of 36 years and a sex-ratio of 2.35. Ultrasound EAT thickness was significantly increased in SpA patients compared with healthy controls (median value of 3.1 mm versus 2.4 mm; p=0.001). EAT thickness was positively correlated with patient-related parameters (age, systolic blood pressure, triglyceride level). Regarding disease-related characteristics, EAT thickness was positively correlated to age at onset of SpA and negatively correlated to chest expansion. Moreover, EAT thickness was significantly associated with radiographic structural damage (syndesmophytes, bony bridging, facet joint arthritis, and mSASSS score). In multivariate linear regression, age at onset of SpA, triglyceride level, and mSASSS were identified as the independent predictive factors of increased EAT thickness in SpA.

SpA patients exhibited significantly more subclinical coronary atherosclerosis than controls. EAT thickness was independently associated with mSASSS score supporting the role of the inflammatory process in cardiovascular risk.

Keywords

Echocardiography, atherosclerosis, spondyloarthritis

Résumé

Introduction : Il existe un intérêt croissant pour le rôle du tissu adipeux épicardique (EAT) en tant que nouveau marqueur de l'athérosclérose coronarienne subclinique. Le but de ce travail était d'identifier les facteurs prédictifs de l'augmentation de l'épaisseur de l'EAT chez les patients atteints de spondylarthrite ankylosante (SpA) sans facteurs de risque cardiovasculaire.

Méthodes : Nous avons mené une étude transversale incluant des patients atteints de SpA et des sujets sains appariés selon l'âge et le sexe sans facteurs de risque cardiovasculaire. Des données générales et biologiques ont été obtenues pour tous les participants. Ainsi que les caractéristiques de la maladie ainsi que les modalités thérapeutiques. Les patients et les groupes témoins ont subi une échocardiographie avec mesure de l'épaisseur EAT.

Résultats : Au total, 47 patients atteints de SpA et 47 témoins sains ont été inclus, avec un âge médian de 36 ans et un sex-ratio de 2,35. L'épaisseur de l'EAT était significativement augmentée chez les patients atteints de SpA par rapport aux témoins sains (valeur médiane de 3,1 mm contre 2,4 millimètre ; p=0,001). L'épaisseur de l'EAT était positivement corrélée avec les paramètres liés au patient (âge, pression artérielle systolique, taux de triglycérides)

En ce qui concerne les caractéristiques liées à la maladie, l'épaisseur de l'EAT était positivement corrélée à l'âge au début de la SpA et négativement corrélée à l'expansion de la poitrine. De plus, l'épaisseur de l'EAT était significativement associée aux dommages structuraux radiographiques

En régression linéaire multivariée, l'âge au début de la SpA, le taux de triglycérides et le mSASSS ont été identifiés comme facteurs prédictifs indépendants de l'augmentation de l'épaisseur de l'EAT dans la SpA.

Conclusions : Les patients atteints de SpA présentaient significativement plus d'athérosclérose coronarienne subclinique que les témoins. L'épaisseur de l'EAT était indépendamment associée au score mSASSS soutenant le rôle du processus inflammatoire dans le risque cardiovasculaire

Mots-clés

Echocardiographie, athérosclérose, spondylarthrite ankylosante

Correspondance

Takwa Mehmli

Rheumatology Department, Charles Nicolle Hospital, Tunis, Tunisia, 1007

Email : mehmlitakwa@gmail.com

INTRODUCTION

Enhanced cardiovascular (CV) disease risk and atherosclerotic events have been well described in Spondyloarthritis (SpA) [1]. The relative risk of CV disease mortality and coronary artery disease (CAD) had reached 1.6-1.9 and 41%, respectively [2]. This CV burden is not fully explained by traditional CV risk factors. The underlying mechanisms of accelerated atherosclerosis in this population are probably multifactorial, including the chronic inflammatory process with increased concentrations of inflammatory cytokines and adipokines [1,3].

Ectopic fat, such as epicardial adipose tissue (EAT) and abdominal visceral fat, have been shown to be associated with atherosclerosis development, independent of traditional CV risk factors [4]. EAT is an ectopic fat located between the myocardium and the visceral layer of the pericardium mainly in the atrioventricular and interventricular grooves. Owing to its endocrine properties with the secretion of inflammatory and pro-atherogenic adipocytokines [5] and paracrine effect on the coronary arteries [6], EAT has emerged as a potential contributor to the pathogenesis of coronary atherosclerosis [7].

EAT is nowadays identified as a novel cardiometabolic risk factor, and increased ultrasound (US) EAT thickness is an independent predictor of risk for CAD [7,8]. Recent data confirmed that the US measurement of EAT thickness was a reliable tool for estimation of coronary atherosclerosis [7,9].

Our previous work supported these findings in SpA by showing that increased EAT thickness was correlated with decreased flow-mediated dilation (FMD) which is the US marker of endothelial dysfunction, the first step of atherosclerosis [10].

This new research is an extended paper based on the previous one [10], and aimed to identify the predictive factors of increased EAT thickness in SpA patients free of CV risk factors.

MATERIALS AND METHODS

Study design and population

We conducted a prospective case-control study between March and September 2021. Patients fulfilling the Assessment of SpondyloArthritis International Society criteria [11,12] were consecutively recruited. Each participant was informed about the study protocol and has given written consent. Institutional ethical committee approval was obtained. Patients with juvenile SpA, enteropathic SpA, psoriatic arthritis or reactive arthritis were not included. Other non-inclusion criteria were : participants aged more than fifty years, using alcohol or cigarettes, having a previous history of CV disease, family history of premature CAD, hypertension (systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg or use of antihypertensives), diabetes mellitus, hypercholesterolemia, hypertriglyceridemia, obesity (body mass index (BMI)>30 kg/m2), kidney failure, active or chronic infection, dysthyroidism, or other concomitant connective or inflammatory disease. Pregnant women, subjects with poor echogenicity making measurement of EAT thickness non evaluable, or who didn't give their informed consent were excluded. The control group included age and gender-matched healthy volunteers with no history of cardiac disease, no traditional CV risk factor and normal physical examination.

Clinical Evaluation

General data (age, gender and BMI) were collected. Arterial blood pressure values (SBP and DBP) were measured after a rest of 10 minutes in the patients and control groups.

Disease-related information's were obtained: age at onset of SpA, disease duration, Ankylosing Spondylitis Disease Activity Score (ASDAS) and Bath Ankylosing Spondylitis Functional Index (BASFI). Spinal mobility distances (cervical rotation, chest expansion, Schöber test), and Bath Ankylosing Spondylitis Mobility Index (BASMI) were measured. Current therapeutic modalities (Non-steroidal anti-inflammatory drugs (NSAIDs), conventional synthetic DMARDs (csDMARDS), or tumor necrosis factor inhibitors (TNFi) were also analyzed.

Laboratory investigations

Blood specimens after 12 hours of fasting were collected from participants at the time of the enrollment. Serum total cholesterol, High-density lipoprotein cholesterol (HDL-C), Low-density lipoprotein cholesterol (LDL-C), triglycerides, fasting glucose, creatinine and C-reactive protein (CRP) levels were measured.

Radiological assessment

At the time of CV assessment, radiographs of the cervical, thoracic, lumbar spine, and pelvis were obtained. Spinal structural lesions were recorded: vertebral squaring, syndesmophytes, Romanus spondylitis, bony bridges, bamboo spine and facet joint arthritis. Structural damage was scored according to the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) and the Bath Ankylosing Spondylitis Radiology Index (BASRI)) [13,14]. Right and left sacroiliitis were recorded according to the modified New York criteria [15]. Sacroiliitis, coxitis, the mSASSS, and the BASRI were scored by a trained radiologist who was blinded to the patient characteristics.

Echocardiographic assessment of epicardial fat thickness

Transthoracic echocardiography was performed for all participants (patients and healthy controls) using a Vivid 9-general electric GE system cardiac US and a high-frequency probe. An echocardiographic examination was performed after 15 minutes of rest in the left lateral decubitus position by an experienced cardiologist. EAT thickness was obtained from the parasternal long-axis view perpendicularly to the right ventricle free wall, in telesystole. EAT was defined as the echo-free space between the outer border of the myocardium and the visceral layer of the pericardium [16]. The EAT thickness was determined as the average of three measurements (One measure per each cardiac cycle for 3 cycles).

Due to the lack of a standardized cut-off value for EAT thickness, it was considered a continuous variable without a limit value in our analysis.

Statistical analysis

Statistical analysis was performed using Statistical Software for the Social Sciences (SPSS) version 25. Categorical data were expressed as percentages and numbers, and quantitative variables were mentioned as medians and interquartile intervals (IQR).

Comparisons between baseline characteristics were carried out by the Mann-Whitney test and Pearson's chi-square test. The Kruskal–Wallis test was used for the comparison of more than three quantitative variables. Spearman's correlation coefficients were used to investigate the relationship between the EAT thickness and patient-related/disease-related parameters.

A multivariate linear regression analysis was performed to investigate independently associated factors to increased EAT thickness in SpA patients. The «Enter» method was chosen. All variables with a p value<0.2 in the univariate linear regression analysis were entered into the multiple linear regression model. The final model was selected based on a high F-test and high R^2 (R-Squared score) with a significant p-value with the observation of the residuals. Statistical significance was indicated by a p value<0.05.

RESULTS

Forty-seven SpA patients met the selection criteria. Among the 47 SpA patients and the 47 matched controls, 70% were male, with a median (IQR) age of 36 years (28-46) and 32 years (26-43), respectively in the patients and control groups. There was no significant difference between the two groups in terms of age, gender, and CV risk factors (BMI, SBP, DBP, total cholesterol, HDL-C, LDL-C, triglyceride, fasting glucose and creatinine serum levels).

In the SpA group, median (IQR) duration of the disease was 11 years (5-16) and ranged between 1 and 32 years. Of the 47 patients, 55% had an active disease according to ASDAS-CRP; and 45% of patients have increased CRP levels . Structural spine damage was seen in 44 patients (94%). Twenty-five patients (53%) had coxitis. Regarding treatment, 92% of patients were under NSAIDs, 51% under csDMARDs (Sulfasalazine (47%), Methotrexate (4%)) and 38% received TNFi. The clinical characteristics and biological findings of the two study groups as well as SpA features are detailed in table 1.

Table 1. Clinical and paraclinical characteristics of the SpA patients and control groups.

	SpA Patients (N=47)	Controls (N=47)	p
Age (years)*	36 (28–46)	32 (26-43)	0,267
Sex-ratio	2.35	2.35	0,589
BMI (Kg/m^2)*	24,5 (20,7-26,8)	24,9 (23-27,2)	0,238
SBP (mmHg)*	121 (110-130)	120 (110-128)	0.357
DBP (mmHg)*	71 (67-78)	70 (65-78)	0.847
Creatinine (*µmol*/l)*	63 (58.5-74)	63 (55-70)	0.342
Total cholesterol (mmol/l)*	3,66 (3,18-4,28)	3.60 (3.46-4.23)	0.904
Triglycerides (mmol/l)*	0,84 (0,79-1,15)	0.92 (0.78-1.06)	0.946
HDL-C (mmol/l)*	1,08 (0,92-1,2)	1.16 (0.99-1.31)	0.052
LDL-C (mmol/l)*	2,17 (1.78-2.6)	2.1 (1.7-2.5)	0.943
Fasting glucose (mmol/l)*	4.93 (4.55-5.1)	4.88 (4.51-5.08)	0.639
Age at onset of SpA (years)*	20 (18-32)	NA	
Disease duration (years)*	11 (5-16)	NA	
ASDAS CRP*	2.18 (1.62-2.91)	NA	
CRP (mg/l)*	6.45 (1.45-19.9)	NA	
BASMI*	1.5 (0-4)	NA	
BASFI*	3 (1.5-5.1)	NA	
BASRI*	3 (2.4)	NA	
mSASSS*	10 (0-37)	NA	
Radiographic sacroiliitis	45/47 (96%)	NA	
Coxitis	25/47 (53%)	NA	
Vertebralsquaring	39/47 (83%)	NA	
Syndesmophytes	21/47 (45%)	NA	
Romanus spondylitis	6/47 (13%)	NA	
Bony bridges	7/47 (15%)	NA	
Bamboo spine	3/47 (6%)	NA	
Facet joint arthritis	16/47 (34%)	NA	

*Values are presented as median and interquartile range.

SpA: spondyloarthritis; p: coefficient of significance; BMI: body mass index; SBP: systolic blood pressure; DBP: Diastolic blood pressure; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index;CRP: C-reactive protein; BASMI: Bath Ankylosing Spondylitis Metrology Index; BASFI: Bath Ankylosing Spondylitis Functionnal Index; BASRI: Bath Ankylosing Spondylitis Radiologic Index;; mSASSS: modified Stoke Ankylosing Spondylitis Spine Score; NA: not applicated.

Echocardiographic examination showed significantly increased EAT thickness in SpA patients compared with healthy controls with a median (IQR) value of 3.1 mm (2.5-4) in SpA patients versus 2.4 mm (2-3) in controls (p=0.001).

Correlation between EAT thickness and patients-related parameters revealed a positive correlation with age, SBP and triglyceride level (table 2). No association was found between EAT thickness and other CV risk-related factors (table 2).

Table 2. Correlations between EAT thickness and patients-related parameters.

	r	p value
Age (years)	0.483	**0.001**
Sex		0.701
BMI (kg/m²)	0.181	0.223
SBP (mmHg)	0.323	**0.028**
DBP (mmHg)	0.270	0.069
Fasting glucose (mmol/l)	0.248	0.104
Total cholesterol (mmol)l)	0.236	0.127
Triglyceride (mmol/l)	0.349	**0.022**
HDL-C (mmol/l)	0.085	0.587
LDL-C (mmol/l)	0.149	0.342
Total cholesterol / HDL-C	0.128	0.418
LDL-C/HDL-C	0.064	0.683
Creatinine (µmol/l)	0,160	0,293

BMI: body mass index ; SBP : systolic blood pressure; DBP : Diastolic blood pressure; HR : heart rate ; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; p :coefficient of significance ; r: association.

Correlations between EAT thickness and SpA-related parameters are shown in table 3. EAT thickness was positively correlated with age at onset of SpA, and negatively correlated with chest expansion. There was no correlation between increased EAT thickness and disease activity, BASFI and BASMI scores. Analysis according to disease activity levels (ASDAS-CRP≥2.1) did not reveal significant differences between the two groups in terms of ASDAS-CRP (p=0.527). Regarding structural radiographic damage, EAT thickness was significantly increased in the presence of syndesmophytes, bony bridging, and facet a joint arthritis. EAT thickness was positively correlated with mSASSS. Patients treated with TNFi had significantly higher values of EAT thickness compared with those treated with NSAIDs or csDMARDs (with a median (IQR) value of 3.95 mm (3.1-4.6) versus 2.7 mm (2.3-3.5); p=0.007).

Table 3. Association between EAT thickness and SpA related parameters.

	r	p value
Age at onset of SpA(years)	0.353	**0.016**
Disease duration (years)	0.219	0.140
ASDAS-CRP	0.212	0.158
CRP (mg/l)	0.151	0.318
BASFI	0.191	0.198
BASMI	0,176	0,242
Chest expansion (cm)	-0.351	**0.016**
BASRI	0.275	0.068
mSASSS	0.458	**0.02**
Radiographic sacroiliitis		0.279
Coxitis		0.605
Vertebral squaring		0.148
Syndesmophytes		**0.005**
Romanus spondylitis		0.415
Bony bridges		**0.022**
Bamboo spine		0.05
Facet joint arthritis		**0.015**

ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CRP: C-reactive protein; BASFI: Bath Ankylosing Spondylitis Functionnal Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; BASRI: Bath Ankylosing Spondylitis Radiologic Index; BASRI: Bath Ankylosing Spondylitis Radiologic Index; mSASSS: modified Stoke Ankylosing Spondylitis Spine Score; p: coefficient of significance; r: association.

Multivariate linear regression suggested that 45.7% of increased EAT thickness in SpA patients would be explained by three variables: age at onset of SpA, triglyceride level, and mSASSS score (R^2=0,457) (table 4). Among these 3 independent risk factors associated with increased EAT thickness; the mSASSS score was the best independent predictor, with a 23% of contribution in the predictive model. Our model concluded then to the following predictive formula of EAT thickness.

Table 4. Multiple linear regression for identifying independent associates of EAT thickness in patients with SpA.

	β	p	95% IC
Age of onset of SpA	0.045	0.008	0.012 – 0.075
Triglyceride level	0,661	0.01	0.168 – 1.143
mSASSS	0,064	0.001	0.03 – 0.091

SpA: spondyloarthritis; mSASSS: modified stoke ankylosing spondylitis spinal score; β : beta coefficient; p: coefficient of significance; IC: 95% interconfidence interval.

Predicted EAT thickness =0,958 + 0,045 * age of onset of SpA + 0,661 * Triglyceride level +0,064 * mSASSS. (Age of onset of SpA: expressed in years/ Triglyceride level: expressed in mmol/L).

DISCUSSION

This cross-sectional study showed that median US EAT thickness was significantly higher in SpA patients than in the matched healthy

controls. Age at onset of SpA, triglyceride level and mSASSS score were independent predictive factors of subclinical coronary atherosclerosis.

Our findings support the hypothesis that SpA patients without CV risk factors display increased predicted subclinical coronary atherosclerosis. US assessment of epicardial fat in SpA has been little studied. To date, eight studies assessing US EAT thickness in SpA have been performed and demonstrated significantly higher values in SpA patients than in the control group, in agreement with our result [17-24]. Table 5 summarizes the main patients' characteristics and US findings of these studies, which included between 26 and 60 SpA patients. This is an additional argument in favor of the representative number of our sample of 47 SpA without CV risk factors.

The median EAT thickness in our SpA patients was the lowest value (3.1 mm (2.5-4)) compared with the EAT thickness measurements published in the literature data, which ranged between 4.35 mm and 7.3 mm (table 5). By reviewing the various reports, we spotted multiple factors that could explain the difference in the results. In fact, age, BMI values, disease activity state and lipid profile which are confounding factors were different among studies. Moreover, smoking was not excluded in studies carried by Üstün N et al, Çaglar SO et al and Öz A et al [18,19,23]. Taking into account that (age, smoking, BMI and lipid profile) are known CV risk factors, this variation could be explained by differences in the clinical and biological characteristics of patients and selection criteria.

Table 5. Main clinical characterisctics and echographic findings of studies concerning EAT thickness in SpA.

	Study group SpA/ Controls	Mean age of SpA patients (years)	CVD risk factors	Disease duration (Years)	BMI (Kg/m²)	Lipid profile (mg/dl)	CRP (mg/l)	ASDAS/ BASDAI	EAT thickness SpA / Controls (mm)	p
Resorlu et al (2014) [17]	40/40	42.7 ± 12.4	_	NS	24.7± 3.6	HDL-C : 55.8 ± 17.4 LDL-C : 94.8 ± 12.8 TG : 101.05 ± 41.9	NS	NS / NS	4.35 ± 1.56/ 3.03 ± 0.94	<0.001
Üstün et al (2014) [18]	26/26	43.7 ± 11.8	Smoking+ (30.8%)	11.83 ± 10.98	28.1±5.3	NS	NS	NS / 4.2 ± 2.1	5.15± 1.13/ 4.11 ± 1.22	0.003
Çaglar et al (2016) [19]	42/40	39.3 ± 8.5	Smoking+ (28.5%)	NS	23.9± 7.9	CT: 175 ± 38 TG : 124 ± 66	NS	NS / NS	7.3 ± 1.5 / 6.3 ± 0.7	<0.01
Boyraz et al (2016) [20]	30/25	38.6 ± 8.3	Smoking, dyslipidemia not mentioned in exclusion criteria	8.8±8	25.18	CT : 174.8 ± 38.03 HDL-C : 47.8 ± 11.8 LDL-C : 99.76 ± 31.61 TG : 127.76 ± 62.95	NS	NS / 2.48 ± 2.21	NS : Higher values in SpA patients	NS
Surucu el al (2018) [21]	38/38	35.42 ± 9.11	Smoking, dyslipidemia not mentioned in exclusion criteria	3.5 ± 2.08	24.90 ± 1.82	CT : 185.21 ± 38.98 HDL-C : 44.79 ± 12.61 LDL-C : 108.89± 28.94 TG : 141.76 ± 93.37	9.9 ± 8.8	NS / 4.57 ± 1.84	4.5 ± 1.7/ 3.7 ± 1.0	0.01
Büyükterzi et al (2019) [22]	50/50	39 (35-45)	_	NS	24.22 ± 3.11	CT: 208 (184- 224) HDL-C:46 (40- 54) LDL-C:138.5 (110-150) TG: 132.50 (87- 170,5)	10.30 (3.33-32.55)	NS / NS 48% had an active disease according to ASDAS	4.75 (3.80-6.05) / 3.50 (3.10-4.00)	<0.001
Öz et al (2020) [23]	43/42	42.8 ± 9.2	Smoking + (55.8%)	9.19 ± 5.54	27.3 ± 4.9	CT: 194.7 ± 29.1 HDL-C: 47.9 ± 10.8 LDL-C: 122.8 ± 25.3 TG : 119.8 ± 61.1	7.28 ± 9.49	2.38 ± 0.77/ 2.91 ± 1.86	4.6 ± 1.5 / 3.3 ± 1.2	<0.001
Demir et al (2020) [24]	60/60	46.6 ± 8.7	Smoking not mentioned in exclusion criteria	3 (1–7)	29.24 ± 5.11	HDL-C : 45.27 ± 9.54 LDL-C: 129.35± 27.03 TG : 152.94 ± 83.44	10 (3.39–14.90)	NS / 4.10 ± 2.22	5.74 ±1.22/ 4.91 ± 1.21	<0.001
Our study	47/47	36 (28 – 46)	_	11 (5-16)	24.5 (20.7-26.8)	CT : 141.5 (122-165) HDL-C : 41.7 (35-46) LDL-C : 83 (68-100)	6.45 (1.5-19.9)	2.18 (1.6-2.9) /2.6 (1.8-3.8)	3.1 (2.5-4)/ 2.4 (2-3)	0.001

SpA: Spondyloarthritis; CVD : cardiovascular disease; +: present; -:absent; BMI : body mass index ; CRP : C-reactive protein ; EAT : epicardial adipose tissue ; ASDAS : Ankylosing Spondylitis Disease Activity Score ; BASDAI : Bath Ankylosing Spondylitis Disease Activity Index ; p : coefficient of significance ; CT : total cholesterol ; LDL-C : LDL cholesterol ; HDL-C : HDL cholesterol ; TG : triglyceride ; NS : not specified.

There is no consensus for the measurement of EAT thickness. MRI is considered the gold standard for the quantification of EAT thickness [25] but is limited by its high cost, cumbersomenesss and limited availability. Recent data concluded that echocardiographic measurement is the best tool for assessment of EAT thickness considering its reproductibility, ease of application, cost-effectiveness and non-invasive nature compared to other imaging modalities and proposed it as a simple and reliable strategy for CV disease risk stratification and prediction of atherosclerotic burden [7,9]. A recent meta-analysis confirmed that US EAT thickness was increased in CAD and the real challenge would be to determine the US threshold of EAT thickness at which there is a linear relationship with the risk of CAD [7]. Majumder R et al suggested an US threshold of EAT thickness >4.65mm as an independent predictor of significant coronary stenosis confirmed by coronary angiography [9]. In the light of these findings, EAT thickness is actually regarded as a surrogate marker of CV risk and increased EAT is an independent predictor of subclinical coronary atherosclerosis. EAT thickness was associated with the presence and severity of CAD [7,26] independently of traditional CV risk factors [27], and correlated with high-risk and unstable coronary plaques [28,29].

Although the present study included young SpA patients (≤50 years) without history of traditional CV risk factors, EAT thickness was positively correlated with age and SBP. In line with our result, Resorlu H et al also reported significant association between EAT thickness and age as well as DBP in 40 SpA patients [17]. Svanteson M et al found that age was the strongest independent predictor of CAD in 86 patients with inflammatory joint disease (rheumatoid arthritis, SpA and psoriatic arthritis) [30]. It seems that age leads to qualitative modifications of the EAT with reduced expression of adiponectin by the EAT [31].

In our study, triglyceride level was identified as an independent predictor of increased EAT thickness in multivariate analysis in SpA patients (β coefficient, 0.661; 95% confidence interval (95% CI), 0.168–1.143; p = 0.01) as it has been reported by Resorlu H et al also [17]. This association is explained by the pathophysiology of ectopic fat depositions. Ectopic lipid storage is associated with insulin resistance, which stimulates lipogenesis de novo and hepatic triglyceride production [32]. The correlation between these patient-related parameters and increased EAT thickness highlights the importance of regular screening of traditional CV risk factors even in young patients with low disease activity.

When looking at disease-related parameters, EAT thickness was correlated to age at onset of SpA, chest expansion and mSASSS. The association between EAT thickness and thoracic spinal mobility has not been studied. In our sample, reduced thoracic spinal mobility was correlated with increased CV risk. Similar to our finding, HamdiW et al and Bodnár N et al demonstrated a negative correlation between carotid intima-media thickness and chest expansion in SpA patients, supporting the relationship between restriction of spinal mobility and subclinical atherosclerosis [33,34]. However, it has been shown that spinal mobility impairment is independently determined both by irreversible spinal radiographic damage in later disease stages and in an early axial SpA by clinical disease activity and active spinal inflammation on MRI [35]. Regarding disease duration, our finding were in contrast to those described by Surucu GD et al and Resorlu H et al, who reported a significant association between EAT and disease duration [17,21]. This may be due to the heterogeneity of disease duration distribution between patients which ranged between 1 and 32 years.

To our knowledge, for the first time in literature, our study determined a powerful association between EAT thickness and radiographic structural damage. EAT thickness was significantly increased in patients with spinal structural lesions (syndesmophytes, bony bridging, apophyseal joint arthritis) and the mSASSS score was identified as the strongest independent predictor of subclinical coronary atherosclerosis. Recent data have suggested a link between structural damage in SpA (syndesmophytes, bony bridging, mSASSS score) and accelerated atherosclerosis as assessed by the carotid intima-media thickness progression [36,37]. Similarly, Kang KY et al demonstrated that the number of syndesmophytes was independently associated with the Framingham risk score (FRS) estimating the 10-year CV disease risk in a cohort of 185 patients with axial SpA without CV risk factor [38]. Coronary atherosclerosis and radiographic progression in SpA seem to share some common pathophysiological substrate. Age, sedentary lifestyle, smoking, and chronic inflammation are established CV risk factors, but also for structural

damage. Chronic activation of the immune system and the inflammatory state underlie the pathophysiology of both atherosclerosis and structural damage. Ectopic fat tissue is the seat of increased secretion of pro-inflammatory molecules with local and systemic action. In fact, EAT over-expresses pro-inflammatory cytokines and pro-atherogenic factors including phospholipase sPLA2-IIA, IL6, adiponectin, and adipokines with an insulin-resistant effect such as resistin and visfatin leading to immune cell activation and inflammation, and contribute to the development and progression of atherosclerosis [6,39,40]. On the other hand, recent data show that adipokines were also correlated the progression spinal progression in SpA [41-45]. The latest study of Rademacher J confirmed that new syndesmophyte formation and mSASSS progression after 4 years in SpA was significantly associated with increased levels of visfatin and leptin over the first 2 years [46].

Furthermore, we determined no significant association between EAT thickness and disease activity (ASDAS-CRP) as well as CRP level in agreement with findings of Surucu GD et al [21], Resorlu H et al [17] and Üstün N et al [18]. In contrast, Büyükterzi Z et al have found ASDAS to be independently associated with EAT thickness in a cohort of 50 newly diagnosed SpA patients ($p<0.001$) [22]. This result may be explained by the low disease activity in the majority of patients and the relatively low CRP level (with a median of 6.45 mg/l).

One other important finding of our study is that patients treated with TNFi exhibited significantly higher values of EAT thickness than those treated with NSAIDs and csDMARDs ($p=0.007$). Available data on the effect of TNFi on CV disease risk show discrepant findings. Some clinical studies have reported their effectiveness in improving carotid intima-media thickness, endothelial dysfunction and arterial stiffness in SpA patients [47,48] and have suggested their protective effect against CV events by dampening inflammation. However, Knowles L et al in a recent systematic review of 60 studies examining the effect of TNFi on Flow-mediated dilation, carotid intima-media thickness and P-wave velocity (PWV) in chronic inflammatory diseases did not found a strong evidence for a beneficial effect on atherosclerosis and this hypothesis remains controversial [49]. Given the small size of our study population (18/47 using TNFi) and its heterogeneity in terms of age and disease duration (with a significantly higher age ($p=0.009$) and disease duration of SpA ($p=0.004$) in the group using TNFi, no conclusions can be drawn.

Despite providing findings of absolute novelty, our study has some limitations. First, the heterogeneity of our study group in terms of age and disease duration (ranging between 18-50 years and 1-32 years, respectively) may lead to interpretation bias. Secondly, it would be highly interesting to assess the inter-observer reproductibility of US measurement of EAT thickness that was unavailable in our study. Third limitation was the lack of standardized cut-off value for EAT thickness, therefore it was considered as a continuous variable. Establishing a reference threshold value in our population would be more relevant. In addition, due to the cross-sectional design of our study, we could not assess causality between studied relationships, hence the interest of futher longitudinal studies. Finally, our study was also limited by the lack of power of significant associations with a correlation coefficient (r) <0.5, which decreases the strength of our conclusions.

CONCLUSION

As an emerging marker of subclinical coronary atherosclerosis, this study provides evidence of significantly increased EAT thickness in young SpA patients. To our knowledge, this is the first study to determine the mSASSS score as independent predictive factor of increased EAT in SpA. This is a further argument supporting that atherosclerosis in SpA is mainly accelerated by chronic inflammation in the absence of any CV risk factor. These findings must be confirmed by further larger prospective studies on EAT thickness and implyearlier treatment and physical therapy in order to prevent radiographic progression and atherosclerotic events.

Author contributions

Methodology: B.T.A and B.M.I and F.A; Formal analysis: B.T.A and M, T; Data curation: M.T and B.M.I; Investigation: B.M.I and F.A; Writing – Original Draft Preparation: M.T; Writing – Review & Editing: B.T.A; Conceptualization: M.I; Supervision: M.I and A.L; Validation: A.L.

Informed consent statement: Written informed consent was obtained from all patients.

Statement of ethics and consent: Our locally appointed ethics committee "Charles Nicolle Hospital local committee" has approved the research protocol. Our study was performed in line with the Declaration of Helsinki.

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