Clinical Rheumatology (2022) 41:3017–3025
https://doi.org/10.1007/s10067-022-06261-5

ORIGINAL ARTICLE

Increased epicardial adipose tissue thickness correlates with endothelial dysfunction in spondyloarthritis

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

Received: 25 May 2022 / Revised: 13 June 2022 / Accepted: 17 June 2022 / Published online: 1 July 2022

Abstract

Introduction We aimed to investigate the relationship between epicardial adipose tissue (EAT) thickness, flow-mediated dilation (FMD), and carotid intima-media thickness (cIMT) in spondyloarthritis (SpA) patients compared to healthy controls.

Methods We performed a cross-sectional study including SpA patients aged ≤ 50 years without traditional cardiovascular risk factors and healthy controls matched for age and gender. Baseline characteristics, laboratory data, and SpA-related parameters were recorded. All participants underwent ultrasound examination with measurement of EAT thickness, FMD, and cIMT by both an experienced cardiologist and radiologist blinded to clinical data. The relationships between the ultrasound measurements were analyzed using Spearman's correlation coefficient and Person correlation.

Results The study included 94 subjects (47 SpA and 47 healthy controls). The sex-ratio was 2.35; the median age of patients was 36 years (IQR: 28–46), and the median disease duration was 11 years (IQR: 5–16). Compared to the control group, SpA patients had significantly higher values of EAT thickness ($p=0.001$) and cIMT ($p<0.0001$). FMD values were significantly lower in SpA patients compared to controls ($p=0.008$). The univariate analysis detected a significant negative association between EAT thickness and FMD ($p=0.026$; $r=-0.325$), and between left cIMT and FMD ($p=0.027$; $r=-0.322$). No association was found between EAT thickness and cIMT.

Conclusion EAT thickness, FMD, and cIMT were significantly impaired in SpA patients compared with healthy controls supporting evidence of accelerated atherosclerosis in SpA. EAT thickness was correlated to endothelial dysfunction suggesting the role of EAT in predicting the early reversible stages of atherosclerosis.

Key Points

- *Spondyloarthritis is associated with impaired subclinical atherosclerosis markers accurately increased epicardial fat and carotid intima-media thickness and endothelial dysfunction.*
- *Increased epicardial fat thickness is correlated with impaired endothelial function in spondyloarthritis patients.*

Keywords Atherosclerosis · Carotid intima-media thickness · Epicardial adipose tissue · Flow-mediated dilation · Spondyloarthritis

Introduction

Spondyloarthritis (SpA), one of the most prevalent chronic rheumatic diseases, is characterized by the occurrence of accelerated atherosclerosis and increased cardiovascular (CV) morbidity and mortality compared with the general population [1]. Although mechanisms of excess CV risk are not fully elucidated, chronic inflammatory process is believed to be the underlying cause contributing to all stages of atherosclerosis [2], including endothelial dysfunction, early atheroma formation, plaque instability, and arterial stiffness. Assessment of subclinical vascular changes before clinical atherosclerotic manifestations is important for CV risk stratification and optimal management as has been recommended by the European League Against Rheumatism (EULAR).

A variety of imaging modalities have been used to assess subclinical atherosclerosis and CV risk. The most

✉ Takwa Mehmli
mehmlitakwa@gmail.com

Extended author information available on the last page of the article

widely recognized and validated marker of subclinical atherosclerosis is carotid intima-media thickness (cIMT) measured non-invasively by high resolution B-mode which has proved its reproducibility and reliability [3]. A second approach is the flow-mediated dilation (FMD) measurement which is also a validated method for the assessment of endothelial dysfunction [4]. Endothelial dysfunction is the key early event in atherogenesis, appearing long before the structural atherosclerotic changes. Recently, studies have identified epicardial adipose tissue (EAT) located between the myocardium and visceral pericardium as an active endocrine organ and a source of several pro-atherogenic and inflammatory adipokines exerting major effects on the vascular system and atherosclerosis pathogenesis [5]. It has been also documented that EAT is rather strongly associated to coronary artery diseases (CAD) than other visceral adipose tissues [6]. Echocardiographic EAT thickness measurement has then emerged as a novel marker of subclinical coronary atherosclerosis and has been proposed as a useful and reliable tool for CV risk stratification [7]. While some reports demonstrated a positive correlation between EAT thickness and cIMT in SpA patients [8, 9], the association between EAT thickness and FMD has not yet been studied in SpA.

Therefore, this study aimed to investigate the relationship between EAT thickness, FMD, and cIMT, as markers of subclinical atherosclerosis in SpA patients compared with those of the healthy population.

Materials and methods

This was a cross-sectional study, enrolling young SpA patients (aged ≤ 50 years) meeting ASAS 2009 criteria for axial and peripheral SpA. Healthy volunteers matched for age and gender were recruited as a control group. Cases of juvenile SpA, enteropathic SpA, psoriatic arthritis, or reactive arthritis were not included. In addition, patients and controls were not included if they had a previous history of congestive heart failure, CAD, cerebrovascular disease, valvulopathy or chronic kidney disease, family history of premature CAD, high blood pressure (systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg), hyperlipidemia, obesity, diabetes mellitus, active infection or connective tissue disease, chronic inflammatory bowel disease, dysthyroidism, liver disease, or nephrotic syndrome capable of affecting lipid metabolism. Subjects using alcohol or cigarettes were also not included.

Before the beginning of the study, all SpA patients and healthy controls gave written informed consent following the principles of the Declaration of Helsinki. The institutional ethics committee approved our study protocol.

Data collection

In both patients and control groups, general data (age, gender and body mass index (BMI)) were collected. Blood pressure and heart rate (HR) were measured after a 10-min rest in a sitting position.

In SpA patients, we recorded disease-related parameters: age at onset of SpA, disease duration, extra-articular features, pain visual analog scale (VAS), bath ankylosing spondylitis global-score (BASG-s), ankylosing spondylitis disease activity score (ASDAS), bath ankylosing spondylitis disease activity index (BASDAI), bath ankylosing spondylitis mobility index (BASMI), bath ankylosing spondylitis functional index (BASFI), Lequesne index and therapeutics data (non-steroidal anti-inflammatory drugs (NSAIDs), conventional synthetic DMARDs (csDMARDs), or tumor necrosis factor α inhibitors (TNFi)).

Laboratory data

Venous blood samples were taken in all participants after 12 h of fasting and were analyzed in order to determine fasting glucose, lipid profile (total cholesterol, triglyceride, HDL-C (high-density lipoprotein-cholesterol), LDL-C (low-density lipoprotein-cholesterol)), creatinine, and C-reactive protein (CRP) levels. Lipid ratios (cholesterol to HDL-C and LDL-C to HDL-C) were also calculated.

Radiographic data

For the assessment of structural radiographic damage, radiographs (cervical and lumbar spine) were scored using the modified stoke ankylosing spondylitis spinal score (mSASSS), and the bath ankylosing spondylitis radiology index (BASRI)). Lequesne's false profile radiograph was obtained to allow diagnosis of coxitis.

Ultrasound examination

Epicardial adipose tissue thickness assessment

A transthoracic echocardiographic examination was performed on all participants by an experienced cardiologist blinded to SpA diagnosis and clinical status, using a Vivid 9-general electric GE system. Subjects were lying in left lateral decubitus position. EAT thickness was measured according to the validated method described by Iacobellis et al. [10].

EAT was identified as the echo-free space between the outer surface of the myocardium and the visceral layer of the pericardium. EAT thickness was measured in parasternal long-axis view, perpendicularly to the free wall of the right ventricle, at end-systole in three cardiac cycles. Maximum EAT thickness was measured from a point on the free wall of the right ventricle and a second point perpendicular to the aortic annulus. We considered the average value of three cardiac cycles.

Flow-mediated dilatation

FMD was measured ultrasonographically by a single experienced radiologist according to the guidelines of the American college of cardiology [11], using a Mindray Resona 7 Z ST + and a 7–10-MHz linear transducer. Measurements were performed in a quiet ambient temperature-controlled room (24 °C) after 6 h of fasting. Caffeine intake, smoking, vasoactive drugs, high-fat foods, vitamin C, and intense exercise were not allowed for 24 h before the brachial study. The right arm was kept immobilized in supination during the entire study. The brachial artery was imaged in the longitudinal plane above the antecubital fossa. A blood pressure cuff was first placed on the forearm. After brachial artery diameter was determined in end-diastole, ischemia was induced by inflating the cuff to a supra systolic level (usually at least 50 mm Hg above the systolic pressure) to obtain arterial occlusion for 5 min. Then, a measurement of the maximal post-ischemic diameter was taken 60 s after cuff deflation. FMD was calculated as the percent change of the artery diameter compared to the baseline value according to the following formula: FMD = (maximum diameter − baseline diameter)/baseline diameter × 100. The percentage of FMD reflects the arterial diameter response to increased blood flow. Lower values indicate impaired endothelial function.

Carotid intima-media thickness

A high-resolution B-mode ultrasonography with the same machine (Mindray Resona 7 ZST +) was used for cIMT measurement. During the examination, the subject lay in a dorsal decubitus position, with the neck extended and slightly turned to the opposite side. The probe was placed parallel to the common carotid artery (CCA). On a longitudinal view, we initially identified the two parallel echogenic lines separated by a hypoechogenic border corresponding to the intima-media complex. The distance between the leading edge of the first echogenic line (lumen-intima interface) of the far wall and the leading edge of the second echogenic line (upper layer of tunica adventitia) was taken as the intima-media thickness. cIMT was measured at three points on the far walls of the left and right CCA 2 cm proximal to the carotid bulb. Then, we calculated the average value of the three locations to obtain the mean cIMT on each side.

We considered that cIMT was increased between 0.7 and 1.5 mm. A spur larger than 1.5 mm inside the vessel lumen was defined as an atherosclerotic plaque [12].

Statistical analysis

We used SPSS software version 25.0 for statistical analysis. Given the lack of standardized cut-off values, we considered in our analysis the EAT thickness and FMD as continuous binary variables. Categorical variables were expressed as percentages. Skewed parameters were expressed as medians and 25th and 75th percentiles. Comparisons were performed using non-parametric tests because of non-normally distributed data: Mann Whitney *U*, Pearson's chi-squared test, and Kruskal–Wallis. Spearman's correlation coefficient and Person correlation were used to analyzing the relationship between the variables. The Cramer's Phi and *V* tests were used to determine the strength of the association. *p*-values < 0.05 were accepted as statistically significant.

Results

A total of 94 subjects were enrolled (47 SpA patients and 47 healthy controls). Baseline clinical and biological characteristics of SpA patients and cross-matched healthy volunteers are listed in Table 1. There was no significant difference between the patients and control groups in terms of age, gender, BMI, and blood pressure. In addition, no difference was found in blood lipid profile, fasting glucose, and renal function. SpA patients had significantly higher levels of CRP ($p = 0.001$).

Disease characteristics

The median age at onset of SpA was 20 years (IQR: 18–32), and the median disease duration was 11 years (IQR: 5–16). Regarding disease activity, median BASDAI and ASDAS-CRP were 2.6 (IQR: 1.8–3.8) and 2.18 (IQR: 1.62–2.91) respectively. High disease activity according to BASDAI and ASDAS-CRP were noted in 21% and 55% of patients, respectively. CRP levels were increased in 21 patients (45%). For structural damage, median mSASSS and BASRI scores were 10 (IQR: 4–15) and 3 (IQR: 2-–), respectively. Hip involvement was noted in 53% of patients. As regard treatment, SpA patients received: NSAIDs (92%), csDMARDs (51%), and TNFi (38%). Table 2 summarizes the main SpA-related parameters.

Table 1 Clinical and biological characteristics in SpA and control groups

	SpA Patients Median (IQR)	Control group Median (IQR)	*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
HR (bpm)	71 (64–79)	70 (62–78)	0.592
Total cholesterol (mmol/l)	3.66 (3.18–4.28)	3.60 (3.46–4.23)	0.904
Triglyceride (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
Total cholesterol / HDL-C	3.48 (2.95–3.97)	3.21 (2.69–3.77)	0.248
LDL-C/HDL-C	1.99 (1.54–2.48)	1.9 (1.43–2.31)	0.339
Fasting glucose (mmol/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
CRP (mg/l)	6.45 (1.45–19.9)	4.1 (1.45–7.25)	**0.001**

HR heart rate, *BMI* body mass index, *p* coefficient of significancy, *SBP* systolic blood pressure, *DBP* Diastolic blood pressure, *SpA* spondyloarthritis, *IQR* interquartile range, *HDL-C* HDL cholesterol, *LDL-C* LDL cholesterol, *CRP* C-reactive protein

Ultrasound assessment

SpA patients exhibited significantly thicker EAT values compared to controls: median EAT thickness was 3.1 mm (IQR: 2.5–4) vs 2.4 mm (IQR: 2–3); ($p=0.001$). FMD was significantly lower in patients group (with a median of 14.6% (IQR: 9–24) vs 18.8% (IQR: 12.8–23.1%); $p=0.008$) (Figs. 1 and 2). Median right, left, and mean cIMT were respectively 0.54 mm (IQR: 0.50–0.63), 0.55 mm (IQR: 0.49–0.61), and 0.55 mm (IQR: 0.48–0.62) in SpA patients and 0.45 mm (IQR: 0.42–0.50), 0.47 mm (IQR: 0.45–0.50), and 0.46 mm (IQR: 0.43–0.50) in healthy controls. Median right, left, and mean cIMT values were significantly higher in SpA patients in comparison with control subjects ($p<0.0001$). Increased cIMT values (cIMT > 0.7 mm) were noted in 8 patients (17%), while no patient had atherosclerotic plaque (cIMT > 1.5 mm).

Table 2 Clinical and biological features related to SpA

	Median	IQR	Range
Age at onset of SpA (years)	20	18–32	16–43
Disease duration (years)	11	5–16	1–32
VAS Pain	50	30–60	0–90
BASG-s	45.5	30–60	10–90
ASDAS-CRP	2.18	1.62–2.91	0.32–4.3
BASDAI	2.6	1.8–3.8	0.2–6.5
BASMI	1.5	0–4	0–7
BASFI	3	1.5–5.1	0.6–8.5
BASRI	3	2.4	0–9
mSASSS	10	0–37	4–15
CRP (mg/l)	6.45	1.45–19.9	0.4–80

IQR interquartile range, *SpA* Spondyloarthritis, *VAS* visual analog scale, *BASG-s* Bath Ankylosing Spondylitis Global score, *ASDAS* Ankylosing Spondylitis Disease Activity Score, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *BASFI* Bath Ankylosing Spondylitis Functionnal Index, *BASRI* Bath Ankylosing Spondylitis Radiologic Index, *BASMI* Bath Ankylosing Spondylitis Metrology Index, *mSASSS* modified Stoke Ankylosing Spondylitis Spine Score, *CRP* C-reactive protein

The analysis of the association between these three ultrasound (US) measurements is summarized in Table 3. We demonstrated a negative correlation between EAT thickness and FMD ($p=0.026$; $r=-0.325$) illustrated in Fig. 3. FMD was also negatively correlated with left cIMT ($p=0.027$; $r=-0.322$). However, there was no significant association between EAT thickness and cIMT values.

Discussion

The present study confirmed firstly the increased CV burden and accelerated atherosclerosis as witnessed in all markers of subclinical atherosclerosis. The three US parameters including EAT thickness, FMD, and cIMT were significantly impaired in a cohort of young SpA patients without CV risk factors compared to age and sex-matched healthy controls.

These findings were consistent with the literature data concerning EAT thickness. To date, 8 case–control studies have recently focused on EAT thickness in SpA patients and found significantly thicker the US EAT values in comparison to the healthy population [8, 9, 13–18].

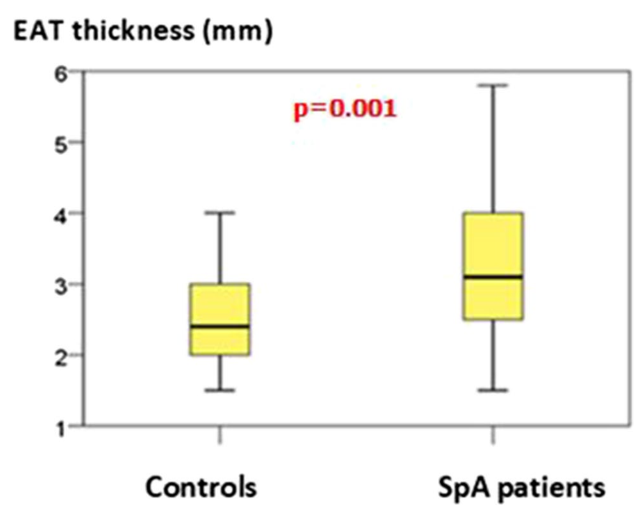

Fig. 1 Comparaison of EAT thickness between the patients and the control groups

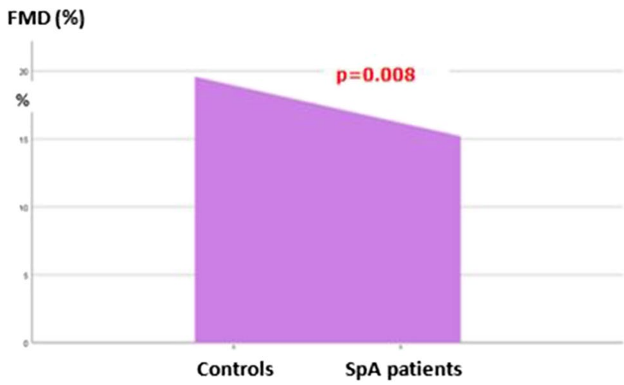

Fig. 2 Comparaison of FMD values between SpA and control groups

Previous reports including 2 meta-analysis demonstrated also significantly increased cIMT values in SpA patients [8, 9, 19–22] and concluded to a subsequent higher risk of subclinical atherosclerosis in line with our result. Regarding endothelial dysfunction, our results were in agreement with the updated data which showed a significant decrease in FMD in SpA patients compared to healthy subjects [23–35].

Interestingly, the novel finding of our study is the negative association between FMD and EAT thickness. To our knowledge, this is the first study to demonstrate a negative correlation between endothelial dysfunction and a marker of subclinical coronary atherosclerosis (EAT thickness) in SpA. Similar results were described in patients with type I diabetic patients [26, 27], and in a cohort of 90 rheumatoid arthritis (RA) patients [28]. EAT thickness was an independent factor influencing endothelial function [26, 27].

There is growing evidence about the physiologic and metabolic significance of EAT. Rather being a passive fat deposit, EAT is involved in lipid and energy homeostasis and is regarded as a functional endocrine organ that secretes several pro-atherogenic mediators accused of contributing to atherosclerosis pathogenesis [10]. Inflammatory adipokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), monocyte, chemoattractant protein-1 (MCP1), IL-1b, plasminogen activator inhibitor-1 (PAI-1), and resistin (which has a mimetic effect and is involved in insulin resistance) were found to be highly expressed by EAT [29] and promoted atherogenesis either by an endocrine effect or by direct diffusion through the vasa vasorum [10]. Previous studies have also demonstrated that EAT thickness is strongly linked to the presence and severity of CAD [30, 31]. Several studies have also shown that endothelial dysfunction especially the reduction in the bioavailability of endothelium-derived nitric oxide (NO) is the initiator and reversible step in atherosclerosis pathogenesis and is one of the best predictors of CVD risk [32]. Recent reports revealed a significant association between endothelial dysfunction and coronary atherosclerosis in patients with intermediate cardiac risk [33]. Brachial artery FMD was independently associated with the presence and extent of subclinical atherosclerosis on coronary computed tomography angiography; it was negatively associated with higher coronary artery calcium (CAC) score, segment involvement score (total number of segments including any plaque), and segment stenosis score in a recent study [33]. Consequently, we suggest that FMD as a surrogate marker of endothelial dysfunction may reflect coronary atherosclerotic burden.

Therefore, EAT thickness as an emerging cardiometabolic factor correlated with the earliest step of atherosclerosis. Adipokines that play an important role in the regulation of the arterial tonus may explain this association. It seems that being higher than the physiological limit, EAT induces a harmful cytokine phenotype. The imbalance between vasodilator adiponectin (which has an anti-atherogenic effect by reducing endothelial activation) and vasoconstrictor resistin has been associated with endothelial dysfunction [34, 35]. In vivo, resistin impaired bradykinin-induced relaxation and authors suggested it may act at a cell signaling point upstream of NO or prostaglandin production [35]. EAT has been also described to affect the endothelium by inducing cell surface expression of adhesion molecules and increasing

Table 3 Associations between echographic parameters

		EAT thickness	Mean cIMT	Right cIMT	Left cIMT	FMD
EAT thickness	**r**	-	0,193	0,098	0,269	**–0,325**
	p	-	0,193	0,511	0,067	**0,026**
Mean cIMT	**r**	-	-	0,941	0,956	–0,284
	p	-	-	**<0,0001**	**<0,0001**	0,053
Right cIMT	**r**	-	-	-	0,802	–0,209
	p	-	-	-	**<0,0001**	0,159
Left cIMT	**r**	-	-	-	-	**–0,322**
	p	-	-	-	-	**0,027**

EAT Epicardial adipose tissue, *cIMT* carotid intima-media thickness, *FMD* Flow mediated dilation, *p* coefficient of significancy, *r* association

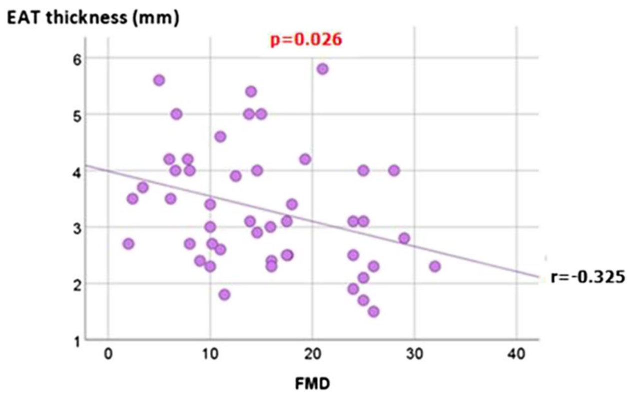

Fig. 3 Association between EAT thickness and FMD

adhesion of monocytes to endothelial cells [36]. Pro-inflammatory cytokines secreted in excess by increased EAT may also explain its association with FMD, by playing a pivotal role in the pathogenesis of endothelial dysfunction [37]. TNF-α over-expression can decrease the release of endothelial NO and cause subsequent impairment of endothelium-dependent vasodilatation [38]. Similarly, administration of IL-6 to mice induced vasoconstriction, increased vascular superoxide production, and impaired endothelium-dependent vasodilatation [39]. These findings raise the question if EAT thickness measurement could be an alternative to reflect endothelial dysfunction.

As we verified in the current study, Bodnàr et al. also demonstrated a significant negative association between cIMT and FMD in a cohort of 43 SpA patients [23].

There are some controversies about the correlation between EAT thickness and cIMT. While some researchers such as Üstün et al. found no evidence of any association [16], others confirmed that EAT thickness was positively correlated with cIMT in SpA patients [8, 9]. In our study, no significant association was obtained between EAT thickness and cIMT. The relationship between EAT and intimal infiltration has been well investigated in non-rheumatic patients, and several authors have demonstrated their strong independent association [40, 41]. EAT thickness was found to be a significant predictor of increased cIMT and the presence of carotid plaque [40, 41]. Athough its threshold value is not yet precisely defined, echocardiographic measured EAT thickness in diastole ≥ 5.0 mm was associated with a significantly higher prevalence of carotid artery plaque in patients with low Framingham risk scores or overweight and has been therefore suggested to identify individuals with a higher risk of having detectable carotid atherosclerosis [42]. Although underlying mechanisms are complex and not fully understood, this association could be explained again by the pro-inflammatory and pro-atherogenic effects of EAT. Increased EAT thickness act associated with adipocytokine imbalance (with up up-regulation of inflammatory adipokines and down-regulation of anti-inflammatory adipokines) [5], affecting coronary and also systemic arteries [43]. IL-6 secreted in excess by EAT induces stimulation of vascular smooth muscle proliferation and subsequently atherosclerotic plaques as well as endothelial cell activation [44]. Oxidative stress with high levels of reactive oxygen species in EAT, increased secretion of group IID secretory phospholipase A2 resulting in accumulation of lipids within atherosclerotic plaques, and high expression of adhesion molecules involved in the pathogenesis of atherosclerosis such as MCP-1, growth-regulated α protein and C–C motif chemokine 5 [36] contribute also to the atherogenicity of EAT [43].

This study has some limitations. First, it was a cross-sectional study; therefore, we cannot conclude to the causal relationship between SpA characteristics and subclinical atherosclerosis markers. Further longitudinal studies involving larger samples are necessary to confirm our results. Second, to date, there are no standardized cut-threshold values for FMD and EAT thickness which has been considered as continuous binary variables in our analysis. Our study group was also heterogeneous in terms of age and disease duration which can cause an interpretation bias.

Conclusion

EAT thickness, FMD, and cIMT as markers of subclinical atherosclerosis were significantly impaired in SpA patients free from CV risk factors in comparison with healthy controls supporting the evidence of inflammatory induced accelerated atherosclerosis. In addition, our study reported the first evidence of a cross-relationship between EAT thickness and endothelial dysfunction suggesting the interest of EAT thickness measurement in diagnosis of early functional atherosclerotic changes.

Declarations

Statement of ethics and consent Our locally appointed ethics committee “Charles Nicolle Hospital local committee” has approved the research protocol. Our institution does not provide us an ethics board approval number. Our study was performed in line with the Declaration of Helsinki.

Consent to participate and to publish Written informed consent was obtained from all patients.

Disclosures None.

References

1. Peters MJ, van der Horst-Bruinsma IE, Dijkmans BA, Nurmohamed MT (2004) Cardiovascular risk profile of patients with spondylarthropathies, particularly ankylosing spondylitis and psoriatic arthritis. Semin Arthritis Rheum 34:585–592. https://doi.org/10.1016/j.semarthrit.2004.07.010
2. Łosińska K, Korkosz M, Kwaśny-Krochin B (2019) Endothelial dysfunction in patients with ankylosing spondylitis. Reumatologia/Rheumatology 57:100–105. https://doi.org/10.5114/reum.2019.84815
3. Kerekes G, Soltész P, Nurmohamed MT, Gonzalez-Gay MA, Turiel M, Végh E, Shoenfeld Y, McInnes I, Szekanecz Z (2012) Validated methods for assessment of subclinical atherosclerosis in rheumatology. Nat Rev Rheumatol 8:224–234. https://doi.org/10.1038/nrrheum.2012.16
4. Moroni L, Selmi C, Angelini C, Meroni PL (2017) Evaluation of endothelial function by flow-mediated dilation: a comprehensive review in rheumatic disease. Arch Immunol Ther Exp (Warsz) 65:463–475. https://doi.org/10.1007/s00005-017-0465-7
5. Shimabukuro M, Hirata Y, Tabata M, Dagvasumberel M, Sato H, Kurobe H, Fukuda D, Soeki T, Kitagawa T, Takanashi S, Sata M (2013) Epicardial adipose tissue volume and adipocytokine imbalance are strongly linked to human coronary atherosclerosis. Arterioscler Thromb Vasc Biol 33:1077–1084. https://doi.org/10.1161/ATVBAHA.112.300829
6. Marchington JM, Mattacks CA, Pond CM (1989) Adipose tissue in the mammalian heart and pericardium: structure, foetal development and biochemical properties. Comp Biochem Physiol B 94:225–232. https://doi.org/10.1016/0305-0491(89)90337-4
7. Ansari MA, Mohebati M, Poursadegh F, Foroughian M, Shamloo AS (2018) Is echocardiographic epicardial fat thickness increased in patients with coronary artery disease? A systematic review and meta-analysis. Electron Physician 10:7249–7258. https://doi.org/10.19082/7249
8. Resorlu H, Akbal A, Resorlu M, Gokmen F, Ates C, Uysal F, Adam G, Aylanc N, Arslan M, İnceer BS (2015) Epicardial adipose tissue thickness in patients with ankylosing spondylitis. Clin Rheumatol 34:295–299. https://doi.org/10.1007/s10067-014-2568-4
9. Surucu GD, Yildirim A, Yetisgin A, Akturk E (2019) Epicardial adipose tissue thickness as a new risk factor for atherosclerosis in patients with ankylosing spondylitis. J Back Musculoskelet Rehabil 32:237–243. https://doi.org/10.3233/BMR-160650
10. Iacobellis G, Willens HJ (2009) Echocardiographic epicardial fat: a review of research and clinical applications. J Am Soc Echocardiogr 22:1311–1319; quiz 1417–8. https://doi.org/10.1016/j.echo.2009.10.013
11. Thijssen DHJ, Bruno RM, van Mil ACCM, Holder SM, Faita F, Greyling A, Zock PL, Taddei S, Deanfield JE, Luscher T, Green DJ, Ghiadoni L (2019) Expert consensus and evidence-based recommendations for the assessment of flow-mediated dilation in humans. Eur Heart J 40:2534–2547. https://doi.org/10.1093/eurheartj/ehz350
12. Choi H, Uceda DE, Dey AK, Mehta NN (2019) Application of Non-invasive Imaging in Inflammatory Disease Conditions to Evaluate Subclinical Coronary Artery Disease. Curr Rheumatol Rep 22:1. https://doi.org/10.1007/s11926-019-0875-0
13. Demir K, Avcı A, Ergulu Esmen S, Tuncez A, Yalcın MU, Yılmaz A, Altunkeser BB (2021) Assessment of arterial stiffness and epicardial adipose tissue thickness in predicting the subclinical atherosclerosis in patients with ankylosing spondylitis. Clin Exp Hypertens 43:169–174. https://doi.org/10.1080/10641963.2020.1833025
14. Çağlar SO, Boyraz İ, Erdem F, Yazici S, Çağlar H, Koç B, Çağlar E, Yazici M (2016) Evaluation of Atrial Conduction Times, Epicardial Fat Thickness and Carotid Intima-Media Thickness in Patients With Ankylosing Spondylitis. Arch Rheumatol 31:353–358. https://doi.org/10.5606/ArchRheumatol.2016.5867
15. Büyükterzi Z, Alpaydin MS, Akkurt HE, Yilmaz H (2019) Epicardial adipose tissue thickness is associated with disease severity in patients with newly- diagnosed ankylosing spondylitis. Kocaeli Med J 8:97–103. https://doi.org/10.5505/ktd.2019.80037
16. Üstün N, Kurt M, Atci N, Yağiz E, Güler H, Turhanoğlu A (2014) Increased epicardial fat tissue is a marker of subclinic atherosclerosis in ankylosing spondylitis. Arch Rheumatol 29:267–272. https://doi.org/10.5606/ArchRheumatol.2014.4606
17. Boyraz I, Caglar S, Erdem F, Yazici M, Yazici S, Koc B, Gunduz R, Karakoyun A (2016) Assessment of relation between neutrophil lympocyte, platelet lympocyte ratios and epicardial fat thickness in patients with ankylosing spondylitis. Med Glas (Zenica) 13:14–17. https://doi.org/10.17392/832-16
18. Öz A, Coşkun H, Çınar T, Efe SÇ, Öz N, Ayça B, Karabağ T, Aytekin E (2020) Evaluation of atrial conduction times and epicardial adipose Ttssue thickness in patients with ankylosing spondylitis. Istanb Med J 21:430–435. https://doi.org/10.4274/imj.galenos.2020.35002
19. Bai R, Zhang Y, Liu W, Ma C, Chen X, Yang J, Sun D (2019) The relationship of ankylosing spondylitis and subclinical atherosclerosis: a systemic review and meta-analysis. Angiology 70:492–500. https://doi.org/10.1177/0003319718814309
20. Cure E, Icli A, Uslu AU, Sakiz D, Cure MC, Baykara RA, Yavuz F, Arslan S, Kucuk A (2018) Atherogenic index of plasma: a useful marker for subclinical atherosclerosis in ankylosing spondylitis: AIP associate with cIMT in AS. Clin Rheumatol 37:1273–1280. https://doi.org/10.1007/s10067-018-4027-0
21. Serdaroğlu Beyazal M, Erdoğan T, Türkyılmaz AK, Devrimsel G, Cüre MC, Beyazal M, Sahin I (2016) Relationship of serum osteoprotegerin with arterial stiffness, preclinical atherosclerosis, and disease activity in patients with ankylosing spondylitis. Clin Rheumatol 35:2235–2241. https://doi.org/10.1007/s10067-016-3198-9
22. Hamdi W, Chelli BM, Zouch I, Ghannouchi MM, Haouel M, Ladeb MF, Kchir MM (2012) Assessment of preclinical atherosclerosis in patients with ankylosing spondylitis. J Rheumatol 39:322–326. https://doi.org/10.3899/jrheum.110792
23. Bodnár N, Kerekes G, Seres I, Paragh G, Kappelmayer J, Némethné ZG, Szegedi G, Shoenfeld Y, Sipka S, Soltész P, Szekanecz Z, Szántó S (2011) Assessment of subclinical vascular disease associated with ankylosing spondylitis. J Rheumatol 38:723–729. https://doi.org/10.3899/jrheum.100668
24. Verma I, Syngle A, Krishan P, Garg N (2017) Endothelial progenitor cells as a marker of endothelial dysfunction and atherosclerosis in ankylosing spondylitis: a cross-sectional study. Int J Angiol 26:36–42. https://doi.org/10.1055/s-0036-1593445
25. Sari I, Okan T, Akar S, Cece H, Altay C, Secil M, Birlik M, Onen F, Akkoc N (2006) Impaired endothelial function in patients with ankylosing spondylitis. Rheumatology 45:283–286. https://doi.org/10.1093/rheumatology/kei145
26. Aydın H, Toprak A, Deyneli O, Yazıcı D, Tarçın Ö, Sancak S, Yavuz D, Akalin S (2010) Epicardial fat tissue thickness correlates with endothelial dysfunction and other cardiovascular risk factors in patients with metabolic syndrome. Metab Syndr Relat Disord 8:229–234. https://doi.org/10.1089/met.2009.0080
27. Aslan AN, Keleş T, Ayhan H, Kasapkara HA, Akçay M, Durmaz T, Sarı C, Baştuğ S, Çakır B, Bozkurt E (2015) The relationship between epicardial fat thickness and endothelial dysfunction in type I diabetes mellitus. Echocardiography 32:1745–1753. https://doi.org/10.1111/echo.12960

28. Temiz A, Gökmen F, Gazi E, Akbal A, Barutçu A, Bekler A, Altun B, Tan YZ, Güneş F, Şen H (2015) Epicardial adipose tissue thickness, flow-mediated dilatation of the brachial artery, and carotid intima-media thickness: associations in rheumatoid arthritis patients. Herz 40:217–224. https://doi.org/10.1007/s00059-014-4140-z
29. Mazurek T, Zhang L, Zalewski A, Mannion JD, Diehl JT, Arafat H, Blat LS, Brien SO, Keiper EA, Johnson AG, Martin J, Goldstein BJ, Shi Y (2003) Human epicardial adipose tissue is a source of inflammatory mediators. Circulation 108:2460–2466. https://doi.org/10.1161/01.CIR.0000099542.57313.C5
30. Ahn SG, Lim HS, Joe DY, Kang SJ, Choi BJ, Choi SY, Yoon MH, Hwang GS, Tahk SJ, Shin JH (2008) Relationship of epicardial adipose tissue by echocardiography to coronary artery disease. Heart 94:e7. https://doi.org/10.1136/hrt.2007.118471
31. Tachibana M, Miyoshi T, Osawa K, Toh N, Oe H, Nakamura K, Naito T, Sato S, Kanazawa S, Ito H (2016) Measurement of epicardial fat thickness by transthoracic echocardiography for predicting high-risk coronary artery plaques. Heart Vessels 31:1758–1766. https://doi.org/10.1007/s00380-016-0802-5
32. Celermajer DS, Sorensen KE, Bull C, Robinson J, Deanfield JE (1994) Endothelium-dependent dilation in the systemic arteries of asymptomatic subjects relates to coronary risk factors and their interaction. J Am Coll Cardiol 24:1468–1474. https://doi.org/10.1016/0735-1097(94)90141-4
33. Lakshmanan S, Shekar C, Kinninger A, Birudaraju D, Dahal S, Onuegbu A, Cherukuri L, Hamal S, Flores F, Dailing C, Roy SK, Budoff M (2020) Association of flow mediated vasodilation and burden of subclinical atherosclerosis by coronary CTA. Atherosclerosis 302:15–19. https://doi.org/10.1016/j.atherosclerosis.2020.04.009
34. Tan KCB, Xu A, Chow WS, Lam MCW, Ai VHG, Tam SCF, Lam KSL (2004) Hypoadiponectinemia is associated with impaired endothelium-dependent vasodilation. J Clin Endocrinol Metab 89:765–769. https://doi.org/10.1210/jc.2003-031012
35. Dick GM, Katz PS, Farias M, Morris M, James J, Knudson JD, Tune JD (2006) Resistin impairs endothelium-dependent dilation to bradykinin, but not acetylcholine, in the coronary circulation. Am J Physiol Heart Circ Physiol 291:H2997-3002. https://doi.org/10.1152/ajpheart.01035.2005
36. Karastergiou K, Evans I, Ogston N, Miheisi N, Nair D, Kaski JC, Jahangiri M, Vidya MA (2010) Epicardial adipokines in obesity and coronary artery disease induce atherogenic changes in monocytes and endothelial cells. Arterioscler Thromb Vasc Biol 30:1340–1346. https://doi.org/10.1161/ATVBAHA.110.204719
37. Zhang C (2008) The role of inflammatory cytokines in endothelial dysfunction. Basic Res Cardiol 103:398–406. https://doi.org/10.1007/s00395-008-0733-0
38. Picchi A, Gao X, Belmadani S, Potter BJ, Focardi M, Chilian WM, Zhang C (2006) Tumor necrosis factor-α induces endothelial dysfunction in the prediabetic metabolic syndrome. Circ Res 99:69–77. https://doi.org/10.1161/01.RES.0000229685.37402.80
39. Wassmann S, Stumpf M, Strehlow K, Schmid A, Schieffer B, Böhm M, Nickenig G (2004) Interleukin-6 induces oxidative stress and endothelial dysfunction by overexpression of the angiotensin II type 1 receptor. Circ Res 94:534–541. https://doi.org/10.1161/01.RES.0000115557.25127.8D
40. Sengul C, Cevik C, Ozveren O, Oduncu V, Sunbul A, Akgun T, Can MM, Semiz E, Dindar I (2011) Echocardiographic epicardial fat thickness is associated with carotid intima-media thickness in patients with metabolic syndrome. Echocardiography 28:853–858. https://doi.org/10.1111/j.1540-8175.2011.01471.x
41. Erdoğan T, Durakoğlugil ME, Çetin M, Altan Kocaman S, Duman H, Çiçek Y, Şatıroğlu Ö (2019) Epicardial adipose tissue predicts carotid intima-media thickness independently of body mass index and waist circumference. Acta Cardiol Sin 35:32–41. https://doi.org/10.6515/ACS.201901_35(1).20180628A
42. Nelson MR, Mookadam F, Thota V, Emani U, Al Harthi M, Lester SJ, Cha S, Stepanek J, Hurst RT (2011) Epicardial fat: an additional measurement for subclinical atherosclerosis and cardiovascular risk stratification? J Am Soc Echocardiogr 24:339–345. https://doi.org/10.1016/j.echo.2010.11.008
43. Iacobellis G (2015) Local and systemic effects of the multifaceted epicardial adipose tissue depot. Nat Rev Endocrinol 11:363–371. https://doi.org/10.1038/nrendo.2015.58
44. Reiss AB, Siegart NM, De Leon J (2017) Interleukin-6 in atherosclerosis: atherogenic or atheroprotective? Clin Lipidol 12:14–23. https://doi.org/10.1080/17584299.2017.1319787

Authors and Affiliations

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

Aicha Ben Tekaya
aicha.bentekaya@fmt.utm.tn

Imtinene Ben Mrad
imtinenebenmrad12@gmail.com

Ahmed Fendri
ahmedfendri541@gmail.com

Seif Boukriba
seifboukriba.sb@gmail.com

Selma Bouden
selma.bouden@gmail.com

Leila Rouached
leila_rouached@hotmail.com

Rawdha Tekaya
tekayarawdha@yahoo.fr

Olfa Saidane
olfa_saidane@yahoo.fr

Ines Mahmoud
ines.mahmoud@fmt.utm.tn

Leila Abdelmoula
abdelmoula_leila@yahoo.fr

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

2 Faculty of Medicine of Tunis, University Tunis El Manar, Tunis, Tunisia

3 Cardiology Department, Habib Thameur Hospital, Tunis, Tunisia

4 Radiology Department, La Rabta Hospital, Tunis, Tunisia