Radiographic structural damage predicted increased epicardial adipose tissue thickness in Spondyloarthritis

Aicha Ben Tekaya
Rheumatology department, Charles Nicolle Hospital, Tunis
Takwa Mehmli (mehmlitakwa@gmail.com)
Rheumatology department, Charles Nicolle Hospital, Tunis
Olfa Saidane
Rheumatology department, Charles Nicolle Hospital, Tunis
Imtinene Ben Mrad
Cardiology department, Habib Thameur Hospital, Tunis
Leila Rouached
Rheumatology department, Charles Nicolle Hospital, Tunis
Selma Bouden
Rheumatology department, Charles Nicolle Hospital, Tunis
Rawdha Tekaya
Rheumatology department, Charles Nicolle Hospital, Tunis
Ahmed Fendri
Radiology department, La Rabta Hospital, Tunis
Ines Mahmoud
Rheumatology department, Charles Nicolle Hospital, Tunis
Leila Abdelmoula
Rheumatology department, Charles Nicolle Hospital, Tunis

Research Article

Keywords: Echocardiography, Atherosclerosis, Spondyloarthritis, Epicardial adipose tissue

Posted Date: May 9th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1612580/v1

Abstract

Introduction:

There is a growing interest in the role of epicardial adipose tissue (EAT) as a novel marker of subclinical coronary atherosclerosis. We aimed to assess EAT thickness in spondyloarthritis (SpA) patients compared with healthy controls and to identify its predictive factors.

Methods:

This was 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.

Results:

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.

Conclusion:

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.

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 and obesity [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]. There is no consensus on the quantification of EAT, different imaging modalities have been proposed. Recent data confirmed that the US measurement of EAT thickness was a reliable tool for estimation of coronary atherosclerosis [7, 9]. However, few studies have focused on EAT and its link to coronary atherosclerosis in patients with SpA.

This work aimed to assess the US measurement of EAT thickness in SpA patients free of CV risk factors compared to healthy controls and to identify the predictive factors of increased EAT thickness.

Methods

Study population

This cross-sectional study was conducted between March and September 2021. Patients who fulfilled the Assessment of SpondyloArthritis International Society criteria [10, 11] and healthy controls were enrolled. Patients with juvenile SpA, enteropathic SpA, psoriatic arthritis or reactive arthritis were not included. Control subjects were age and gender-matched healthy volunteers, recruited from medical and paramedical staff.

Non-inclusion criteria for patients and controls 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) [12], diabetes mellitus, hypercholesterolemia, hypertriglyceridemia, obesity (body mass index (BMI)>30

kg/m^2), 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. Institutional ethical committee approval was obtained. Each participant was informed about the study protocol and has given written consent.

Clinical data

General data (age, gender, BMI, waist circumference and hip circumference) were collected. Arterial blood pressure values (SBP and DBP) were measured after a rest of 10 minutes as well as heart rate (HR) in the patients and control groups.

Disease-related informations were obtained: age at onset of SpA, disease duration, extra-articular features, HLA-B27 status, axial or peripheral form of SpA, and disease activity scores: Ankylosing Spondylitis Disease Activity Score (ASDAS) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). Spinal mobility distances (cervical rotation, chest expansion, Schöber test), and Bath Ankylosing Spondylitis Mobility Index (BASMI) were measured. Functional impairment was assessed by Bath Ankylosing Spondylitis Functional Index (BASFI). Current therapeutic modalities (Non-steroidal anti-inflammatory drugs (NSAIDs), conventional synthetic DMARDs (csDMARDS), or tumor necrosis factor inhibitors (TNFi) were also analyzed.

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.

Biological data

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.

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, at the end of the systole. 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).

Intra-observer reproductibility was measured in 20 patients. We concluded a good reproductibility with kappa concordance coefficient: k=0,654 (p=0,001).

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. Thus, the study population was composed of two groups: the patients group (n=47) and the control group (n=47). 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, BMI and HR. Regarding characteristics related to CV risk, no subject had SBP ≥140 mmhg and/or DBP ≥90 mmHg. Laboratory findings showed increased total cholesterol and triglyceride levels in 2 and 3 patients respectively and fasting glucose level above the normal range in one patient. However, no significant differences were found in terms of total cholesterol, HDL-C, LDL-C, triglyceride, fasting glucose and creatinine serum levels. The clinical and biological data of the two groups are shown in table 1.

In the patients' group, median (IQR) duration of the disease was 11 years (5-16) and ranged between 1 and 32 years. The disease features of SpA patients are detailed in table 2.Median (IQR) BASDAI and ASDAS-CRP scores were 2.6 (1.8-3.8) and 2.18 (1.62-2.91), respectively. Of the 47 patients, 21% had an active disease according to BASDAI and 55% had an active disease according to ASDAS-CRP. Median (IQR) CRP was 6.45 mg/l (1.5-19.9) and 45% of patients have increased CRP levels. Extra-articular features were: restrictive pattern (n=12), first degree atrioventricular block (n=6), right branch block (n=2), uveitis (n=7), xerophtalmia (n=3) and renal involvement (n=6). Renal involvement was as follows: kidney stones (n=2), tubulo-interstitial nephritis (n=2), IgA nephropathy (n=1) and AA amyloidosis (n=1); with normal kidney function and preserved glomerular filtration rate in all patients.

Structural spine damage was seen in 44 patients (94%) as follows: vertebral squaring (83%), syndesmophytes (45%), Romanus spondylitis (13%), bony bridges (15%), bamboo spine (6%) and facet joint arthritis (34%). Median (IQR) mSASSS and BASRI were 10 (4-15) and 3 (2-4), respectively. 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.

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 (p=0.001; r=0.483), SBP (p=0.028; r=0.323) and triglyceride level (p=0.022) (table 3). No association was found between EAT thickness and other CV risk-related factors (table 3).

Concerning disease-related characteristics, EAT thickness was positively correlated with age at onset of SpA (p=0.016; r=0.353), and negatively correlated with chest expansion (p=0.016; r=-0.351).There was no correlation between increased EAT thickness and disease activity, BASFI and BASMI scores. Analysis according to disease activity levels (BASDAI≥4 or ASDAS-CRP≥2.1) did not reveal significant differences between the two groups in terms of BASDAI (p=0.095) and ASDAS-CRP (p=0.527) scores. Patients with renal involvement had higher values of EAT thickness (4.60 mm versus 3.05 mm), without significant difference (p=0.05). Correlations between EAT thickness and SpA-related parameters are shown in table 4. Regarding structural radiographic damage, EAT thickness was significantly increased in the presence of syndesmophytes (p=0.005), bony bridging (p=0.022), and facet a joint arthritis (p=0.015).EAT thickness was positively correlated with mSASSS (p=0.002; r=0.458). 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).

Multivariate linear regression suggested that predictive model 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 5). 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.

Discussion

This cross-sectional study showed that median US EAT thickness was significantly higher in SpA patients than in the matched healthy controls (p = 0.001). This finding supports 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. Table 6 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 6). In fact, further analysis found that patients included in these studies were older than our SpA sample (mean age 38.6–46.6 years versus 36 years) [17–23] have higher values of BMI [17, 22, 23], higher levels of total cholesterol, LDL-C and triglyceride [17–21, 23–24] and higher disease activity [17, 19, 22, 24]. Moreover, smoking was not excluded in studies carried by Üstün et al, Çaglar et al and Öz et al [18, 22, 23]. Taking into account that (age, smoking, BMI and lipid profile) were known CV risk factors, this variation could be explained by differences in the clinical and biological characteristics of patients and selection criteria.

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, cumbersomeness 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]. R Majumder et al suggested an US threshold of EAT thickness > 4.65 mm as an independent predictor of significant coronary stenosis confirmed by coronary angiography [18]. 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 et al also reported significant association between EAT thickness and age as well as DBP in 40 SpA patients (19). Svanteson 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 et al also [19]. 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, Hamdi et al and Bodnár 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 et al and Resorlu et al, who reported a significant association between EAT and disease duration [19, 24]. 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 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 with an enhanced CV risk and 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 scores (BASDAI and ASDAS-CRP) as well as CRP level in agreement with findings of Surucu et al [24], Resorlu et al [19] and Üstün et al [22]. In contrast, Büyükterzi et al have found ASDAS to be independently associated with EAT thickness in a cohort of 50 newly diagnosed SpA patients (p < 0.001) [20]. 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 [44, 47, 49], and have suggested their protective effect against CV events by dampening inflammation. However, Knowles 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 [50].

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. Second 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.

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 imply earlier treatment and physical therapy in order to prevent radiographic progression and atherosclerotic events.

Declarations

Funding:

No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

Competing Interests:

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions:

Takwa Mehmli has drafted the work.

Aicha Ben Tekaya and Imtinene Ben Mrad have substantively revised the work.

Ahmed Fendri has made substantial contributions to the data collection.

Olfa Saidane, Leila Rouached and Salma Bouden have made substantial contributions to the work conception.

Raoudha Tekaya , Ines Mahmoud and Leila Abdelmoula have made substantial contributions to the design of the work.

All authors read and approved the final manuscript.

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.

References

1. Toussirot E. The Risk of Cardiovascular Diseases in Axial Spondyloarthritis. Current Insights. Front Med. 2021;8:782150; https://doi.org/10.3389/fmed.2021.782150.
2. Ungprasert P, Sriv.ali N, Kittanamongkolchai W. Risk of coronary artery disease in patients with ankylosing spondylitis: a systematic review and meta-analysis.Ann Transl Med. 2015; 3(4):51; https://doi.org/10.3978/j.issn.2305-5839.2015.02.05.
3. Bai R, Zhang Y, Liu W, et al.The Relationship of Ankylosing Spondylitis and Subclinical Atherosclerosis: A Systemic Review and Meta-Analysis. Angiology. 2019; 70(6):492–500; https://doi.org/10.1177/0003319718814309.
4. Ding J, Hsu FC, Harris TB, et al. The association of pericardial fat with incident coronary heart disease: the Multi-Ethnic Study of Atherosclerosis (MESA).Am J Clin Nutr. 2009; 90(3):499–504; https://doi.org/10.3945/ajcn.2008.27358.

5. Mazurek T, Zhang L, Zalewski A, et al.Human epicardial adipose tissue is a source of inflammatory mediators. Circulation. 2003 ; 108(20):2460–6; https://doi.org/10.1161/01.CIR.0000099542.57313.C5.
6. Sacks HS, Fain JN. Human epicardial adipose tissue: a review. Am Heart J. 2007; 153(6):907–17; https://doi.org/10.1016/j.ahj.2007.03.019.
7. Ansari MA, Mohebati M, Poursadegh F, Foroughian M, Shamloo AS. Is echocardiographic epicardial fat thickness increased in patients with coronary artery disease? A systematic review and meta-analysis. Electron Physician. 2018 ;10(9):7249–58; https://doi.org/10.19082/7249.
8. Jeong JW, Jeong MH, Yun KH, et al. Echocardiographic epicardial fat thickness and coronary artery disease. Circ J Off J Jpn Circ Soc. 2007;71(4):536–9; https://doi.org/10.1253/circj.71.536.
9. Majumder AR, Rahman MA, Momen A, et al.Association of Echocardiographic Epicardial Fat Thickness with the Angiographic Severity of Coronary Artery Disease in Patients with Acute Coronary Syndrome. Mymensingh Med J MMJ. 2022; 31(1):142–8.
10. Rudwaleit M, van der Heijde D, Landewé R, et al. The Assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general.Ann Rheum Dis. 2011; 70(1):25–31; https://doi.org/10.1136/ard.2010.133645.
11. Rudwaleit M, van der Heijde D, Landewé R, et al.The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis. 2009; 68(6):777–83; https://doi.org/10.1136/ard.2009.108233.
12. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018; 39(33):3021–104; https://doi.org/10.1093/eurheartj/ehy339.
13. Creemers MCW, Franssen MJ a. M, van't Hof MA, Gribnau FWJ, van de Putte LBA, van Riel PLCM. Assessment of outcome in ankylosing spondylitis: an extended radiographic scoring system. Ann Rheum Dis. 2005; 64(1):127–9; https://doi.org/10.1136/ard.2004.020503.
14. MacKay K, Mack C, Brophy S, Calin A. The Bath Ankylosing Spondylitis Radiology Index (BASRI): a new, validated approach to disease assessment. Arthritis Rheum. 1998; 41(12):2263–70; https://doi.org/10.1002/1529-0131(199812)41:12<2263::AID-ART23>3.0.CO;2-I
15. Linden SVD, Valkenburg HA, Cats A. Evaluation of Diagnostic Criteria for Ankylosing Spondylitis. Arthritis Rheum. 1984; 27(4):361–8; https://doi.org/10.1002/art.1780270401.
16. Iacobellis G, Willens HJ. Echocardiographic epicardial fat: a review of research and clinical applications. J Am Soc Echocardiogr Off Publ Am Soc Echocardiogr. 2009; 22(12):1311–9; quiz 1417–8. https://doi.org/10.1016/j.echo.2009.10.013.
17. Demir K, Avcı A, Ergulu Esmen S, et al. Assessment of arterial stiffness and epicardial adipose tissue thickness in predicting the subclinical atherosclerosis in patients with ankylosing spondylitis. Clin Exp Hypertens. 2021; 43(2):169–74; https://doi.org/10.1016/j.echo.2009.10.013.
18. Çağlar SO, Boyraz İ, Erdem F, et al. Evaluation of Atrial Conduction Times, Epicardial Fat Thickness and Carotid Intima-Media Thickness in Patients With Ankylosing Spondylitis. Arch Rheumatol. 2016; 31(4):353–8; https://doi.org/10.5606/ArchRheumatol.2016.5867.
19. Resorlu H, Akbal A, Resorlu M, et al. Epicardial adipose tissue thickness in patients with ankylosing spondylitis. Clin Rheumatol. 2015; 34(2):295–9; https://doi.org/10.1007/s10067-014-2568-4.
20. Büyükterzi Z, Alpaydin MS, Akkurt HE, Yilmaz H. Epicardial adipose tissue thickness is associated with disease severity in patients with newly-diagnosed ankylosing spondylitis. Kocaeli Med J. 2019;8(1):97–103.
21. Boyraz I, Caglar S, Erdem F, et al. Assessment of relation between neutrophil lympocyte, platelet lympocyte ratios and epicardial fat thickness in patients with ankylosing spondylitis. Med Glas Off Publ Med Assoc Zenica-Doboj Cant Bosnia Herzeg. 2016; 13:14–7; https://doi.org/10.17392/832-16.
22. Üstün N, Kurt M, Atci N, Yağiz E, Güler H, Turhanoğlu A. Increased Epicardial Fat Tissue Is a Marker of Subclinic Atherosclerosis in Ankylosing Spondylitis.Arch Rheumatol. 2014;29(4):267–72.
23. Öz A, Coşkun H, Çınar T, et al.Evaluation of Atrial Conduction Times and Epicardial Adipose Tissue Thickness in Patients with Ankylosing Spondylitis. Istanb Med J. 2020; 21(6):430–5.
24. Surucu GD, Yildirim A, Yetisgin A, Akturk E. Epicardial adipose tissue thickness as a new risk factor for atherosclerosis in patients with ankylosing spondylitis. J Back Musculoskelet Rehabil. 2019;32(2):237–43; https://doi.org/10.3233/BMR-160650.
25. Bertaso AG, Bertol D, Duncan BB, Foppa M. Epicardial fat: definition, measurements and systematic review of main outcomes.Arq Bras Cardiol. 2013; 101(1):e18-28; https://doi.org/10.5935/abc.20130138.
26. Ahn SG, Lim HS, Joe DY, et al.Relationship of epicardial adipose tissue by echocardiography to coronary artery disease. Heart Br Card Soc. 2008 ; 94(3):e7; https://doi.org/10.1136/hrt.2007.118471.
27. Mahabadi AA, Berg MH, Lehmann N, et al. Association of epicardial fat with cardiovascular risk factors and incident myocardial infarction in the general population: the Heinz Nixdorf Recall Study. J Am Coll Cardiol. 2013; 61(13):1388–95; https://doi.org/10.1016/j.jacc.2012.11.062.
28. Tachibana M, Miyoshi T, Osawa K, et al. Measurement of epicardial fat thickness by transthoracic echocardiography for predicting high-risk coronary artery plaques. Heart Vessels. 2016; 31(11):1758–66; https://doi.org/10.1007/s00380-016-0802-5.

29. Aprigliano G, Scuteri L, Iafelice I, et al. Epicardial adipose tissue thickness and acute coronary syndrome: a matter of how much or how? Int J Cardiol. 2015; 199:8–9; https://doi.org/10.1016/j.ijcard.2015.06.168.
30. Svanteson M, Rollefstad S, Kløw NE, et al. Associations between coronary and carotid artery atherosclerosis in patients with inflammatory joint diseases. RMD Open. 2017;3(2):e000544; https://doi.org/10.1136/rmdopen-2017-000544
31. Fei J, Cook C, Blough E, Santanam N. Age and sex mediated changes in epicardial fat adipokines. Atherosclerosis. 2010 ; 212(2):488–94; https://doi.org/10.1016/j.atherosclerosis.2010.06.044.
32. Snel M, Jonker JT, Schoones J, et al. Ectopic fat and insulin resistance: pathophysiology and effect of diet and lifestyle interventions. Int J Endocrinol. 2012; 983814; https://doi.org/10.1155/2012/983814.
33. Hamdi W, Chelli Bouaziz M, Zouch I, et al. Assessment of preclinical atherosclerosis in patients with ankylosing spondylitis. J Rheumatol. 2012; 39(2):322–6; https://doi.org/10.3899/jrheum.110792.
34. Bodnár N, Kerekes G, Seres I, et al. Assessment of subclinical vascular disease associated with ankylosing spondylitis. J Rheumatol. 2011; 38(4):723–9; https://doi.org/10.3899/jrheum.100668.
35. Carvalho PD, Ruyssen-Witrand A, Fonseca J, Marreiros A, Machado PM. Determining factors related to impaired spinal and hip mobility in patients with axial spondyloarthritis: longitudinal results from the DESIR cohort.RMD Open. 2020; 6(3):e001356; https://doi.org/10.1136/rmdopen-2020-001356.
36. Ladehesa-Pineda ML, Arias de la Rosa I, López Medina C, et al.Assessment of the relationship between estimated cardiovascular risk and structural damage in patients with axial spondyloarthritis. Ther Adv Musculoskelet Dis. 2020;12:1759720X20982837; https://doi.org/10.1177/1759720X20982837.
37. Giollo A, Dalbeni A, Cioffi G, et al. Factors associated with accelerated subclinical atherosclerosis in patients with spondyloarthritis without overt cardiovascular disease. Clin Rheumatol. 2017; 36(11):2487–95; https://doi.org/10.1007/s10067-017-3786-3.
38. Kang KY, Her YH, Ju JH, Hong YS, Park SH. Radiographic progression is associated with increased cardiovascular risk in patients with axial spondyloarthritis.Mod Rheumatol. 2016; 26(4):601–6; https://doi.org/10.3109/14397595.2015.1119348.
39. Gaborit B, Dutour A. Le tissu adipeux épicardique : un nouveau tissu à prendre en compte. Médecine des Maladies Métaboliques. 2012;6(3):190-4.
40. Gruzdeva OV, Dyleva YA, Belik EV, et al.Relationship between Epicardial and Coronary Adipose Tissue and the Expression of Adiponectin, Leptin, and Interleukin 6 in Patients with Coronary Artery Disease. J Pers Med. 2022;12(2):129; https://doi.org/10.3390/jpm12020129.
41. Genre F, Rueda-Gotor J, Remuzgo-Martínez S, et al. Omentin: a biomarker of cardiovascular risk in individuals with axial spondyloarthritis. Sci Rep. 2020;10:9636; https://doi.org/10.1038/s41598-020-66816-x.
42. Rueda-Gotor J, López-Mejías R, Remuzgo-Martínez S, et al. Vaspin in atherosclerotic disease and cardiovascular risk in axial spondyloarthritis: a genetic and serological study. Arthritis Res Ther. 2021;23(1):111; https://doi.org/10.1186/s13075-021-02499-7.
43. Gonzalez-Lopez L, Fajardo-Robledo NS, Miriam Saldaña-Cruz A, et al. Association of adipokines, interleukin-6, and tumor necrosis factor-αconcentrations with clinical characteristics and presence of spinal syndesmophytes in patients with ankylosing spondylitis: A cross-sectional study. J Int Med Res. 2017; 45(3):1024–35; https://doi.org/10.1177/0300060517708693.
44. Kim KJ, Kim JY, Park SJ, et al. Serum leptin levels are associated with the presence of syndesmophytes in male patients with ankylosing spondylitis. Clin Rheumatol. 2012; 31(8):1231–8; https://doi.org/10.1007/s10067-012-1999-z.
45. Syrbe U, Callhoff J, Conrad K, et al. Serum adipokine levels in patients with ankylosing spondylitis and their relationship to clinical parameters and radiographic spinal progression. Arthritis Rheumatol Hoboken NJ. 2015; 67(3):678–85; https://doi.org/10.1002/art.38968.
46. Rademacher J, Siderius M, Gellert L, et al. Baseline serum biomarkers of inflammation, bone turnover and adipokines predict spinal radiographic progression in ankylosing spondylitis patients on TNF inhibitor therapy. Semin Arthritis Rheum. 2022; 53:151974; https://doi.org/10.1016/j.semarthrit.2022.151974.
47. Angel K, Provan SA, Fagerhol MK, et al. Effect of 1-year anti-TNF-αtherapy on aortic stiffness, carotid atherosclerosis, and calprotectin in inflammatory arthropathies: a controlled study. Am J Hypertens. 2012; 25(6):644–50; https://doi.org/10.1038/ajh.2012.12.
48. Hokstad I, Deyab G, Wang Fagerland M, et al. Tumor necrosis factor inhibitors are associated with reduced complement activation in spondylarthropathies: An observational study. PloS One. 2019;14(7):e0220079; https://doi.org/10.1371/journal.pone.0220079.
49. Végh E, Kerekes G, Pusztai A, et al. Effects of 1-year anti-TNF-αtherapy on vascular function in rheumatoid arthritis and ankylosing spondylitis. Rheumatol Int. 2020; 40(3):427–36; https://doi.org/10.1007/s00296-019-04497-0.
50. Knowles L, Nadeem N, Chowienczyk PJ. Do anti-tumour necrosis factor-α biologics affect subclinical measures of atherosclerosis and arteriosclerosis? A systematic review. Br J Clin Pharmacol. 2020; 86(5):837–51; https://doi.org/10.1111/bcp.14215.

Tables

Table 1

Clinical and laboratory characteristics of the patients and control groups.

	SpA Patients Median (IQR)	Controls Median (IQR)	p
Age (years)	36 (28–46)	32 (26-43)	0,267
Sex-ratio	2.35	2.35	0,589
Weight (Kg)	69 (56-80)	80 (65-83)	**0,021**
Height (m)	1,70 (1,63-1,75)	1,72 (1,67-1,80)	0,054
BMI (Kg/m^2)	24,5 (20,7-26,8)	24,9 (23-27,2)	0,238
Waist circumference (cm)	88 (82-97)	79 (72-88)	**<0,0001**
Hip circumference (cm)	100 (91-97)	99 (87-107)	0,396
HR (bpm)	71 (64-79)	70 (62-78)	0.592
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

HR : heart rate ; BMI : body mass index ; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol, bpm: beats per minute; SBP: systolic blood pressure; DBP: Diastolic blood pressure; p :coefficient of significance ; SpA : spondyloarthritis ; IQR : interquartile range.

Table 2

Clinical characteristics and laboratory findings of the SpA group.

		n	%	Median (IQR)	Min-Max
Age at onset of SpA (years)				20 (18-32)	16-43
HLA status (positive)		10	21		
Disease duration (years)				11 (5-16)	1-32
SpA form	Axial SpA	27	58		
	Peripheral SpA	1	2		
	Axial and peripheral SpA	19	40		
ASDAS CRP				2.18 (1.62-2.91)	0.32-4.3
BASDAI				2.6 (1.8-3.8)	0.2-6.5
CRP (mg/l)				6.45 (1.45-19.9)	0.4-80
BASMI				1.5 (0-4)	0-7
Occiput-wall distance (cm)				3 (2-5)	0-30
Chin-manubrium distance (cm)				0 (0-2)	0-10
Right tragus-acromion distance (cm)				10 (9-14)	7-22
Left tragus-acromion distance (cm)				11 (9-14)	8-22
Right chin-acromion distance (cm)				10 (9-14)	7-20
Left chin-acromion distance (cm)				10 (9-15)	7-20
Chest expansion (cm)				4 (3-5)	2-6
Schöber test (cm)				3 (2-5)	1-5
BASFI				3 (1.5-5.1)	0.6-8.5
BASRI				3 (2.4)	0-9
mSASSS				10 (0-37)	4-15
Radiographic sacroiliitis		45	96		
Coxitis		25	53		
Vertebral squaring		39	83		
Syndesmophytes		21	45		
Romanus spondylitis		6	13		
Bony bridges		7	15		
Bamboo spine		3	6		
Facet joint arthritis		16	34		

IQR: interquartile range; 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; SpA: spondyloarthritis; IQR: interquartile range; %: percentage; n: number.

Table 3

Correlations between EAT thickness and patients-related parameters.

	p value	r
Age (years)	**0.001**	0.483
Sex	0.701	
Weight (Kg)	0,669	0,064
BMI (kg/m^2)	0.223	0.181
Waist circumference (cm)	0.114	0.234
Hip circumference (cm)	0.451	0.113
SBP (mmHg)	**0.028**	0.323
DBP (mmHg)	0.069	0.270
HR (bpm)	0,985	0.003
Fasting glucose (mmol/l)	0.104	0.248
Total cholesterol (mmol)l)	0.127	0.236
Triglyceride (mmol/l)	**0.022**	0.349
HDL-C (mmol/l)	0.587	0.085
LDL-C (mmol/l)	0.342	0.149
Total cholesterol / HDL-C	0.418	0.128
LDL-C/HDL-C	0.683	0.064
Creatinine (µmol/l)	0,293	0,160

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

Table 4

Association between EAT thickness and SpA related parameters.

	p value	r
Age at onset of SpA (years)	**0.016**	0.353
Disease duration (years)	0.140	0.219
HLA-B27 status	0.420	
ASDAS-CRP	0.158	0.212
BASDAI	0.068	0.269
CRP (mg/l)	0.318	0.151
BASFI	0.198	0.191
BASMI	0,242	0,176
Occiput-wall distance (cm)	0.138	0.220
Chin-manubrium distance (cm)	0.304	0.153
Right tragus-acromion distance (cm)	0.218	0.183
Left tragus-acromion distance (cm)	0.252	0.170
Right chin-acromion distance (cm)	0.311	0.151
Left chin-acromion distance (cm)	0.327	0.146
Chest expansion (cm)	**0.016**	-0.351
Schöber test (cm)	0.244	-0.175
BASRI	0.068	0.275
mSASSS	**0.02**	0.458
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; BASFI: Bath Ankylosing Spondylitis Functionnal Index; BASRI: Bath Ankylosing Spondylitis Radiologic Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; BASRI: Bath Ankylosing Spondylitis Radiologic Index; mSASSS: modified Stoke Ankylosing Spondylitis Spine Score; CRP: C-reactive protein; SpA: spondyloarthritis; p: coefficient of significance; r: association.

Table 5

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; 95% IC: 95% interconfidence interval; p: coefficient of significance.

Table 6

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

	Study group SpA/Controls	Mean age of SpA patients (years)	CV risk factors	Disease duration (Years)	BMI (Kg/m^2)	Lipid profile (mg/dl)	CRP (mg/l)	ASDAS/ BASDAI	EAT thickness SpA / Controls (mm)	p
Demir et al (2020) [18]	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
Çaglar et al (2016) [19]	42/40	39.3 ± 8.5	Smoking+ (28.5%)	NS	23.9±7.9	TC: 175 ± 38 TG : 124 ± 66	NS	NS / NS	7.3 ± 1.5 / 6.3 ± 0.7	<0.01
Resorlu et al (2014) [20]	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
Büyükterzi et al (2019) [21]	50/50	39 (35-45)	_	NS	24.22 ± 3.11	TC: 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
Boyraz et al (2016) [22]	30/25	38.6 ± 8.3	Smoking, dyslipidemia not mentioned in exclusion criteria	8.8±8	25.18	TC : 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
Üstün et al (2014) [23]	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

Öz et al (2020) [24]	43/42	42.8±9.2	Smoking + (55.8%)	9.19±5.54	27.3 ± 4.9	TC: 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
Surucu el al (2018) [25]	38/38	35.42 ± 9.11	Smoking, dyslipidemia not mentioned in exclusion criteria	3.5 ± 2.08	24.90 ± 1.82	TC : 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
Our study	47/47	36 (28 – 46)	_	11 (5-16)	24.5 (20.7-26.8)	TC : 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; CV : cardiovascular; +: 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 ; TC : total cholesterol ; LDL-C : LDL cholesterol ; HDL-C : HDL cholesterol ; TG : triglyceride ; NS : not specified.