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EPICARDIAL FAT THICKNESS INCREASE IN PATIENTS WITH SEBORRHEIC DERMATITIS AS A CLINICAL BIOMARKER OF CARDIO-METABOLIC RISK

ZWIĘKSZENIE GRUBOŚCI NASIERDZIOWEJ TKANKI TŁUSZCZOWEJ U PACJENTÓW Z ŁOJOTOKOWYM ZAPALENIEM SKÓRY JAKO BIOMARKER KLINICZNY RYZYKA SERCOWO-METABOLICZNEGO

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Summary

Background. Seborrheic dermatitis (SD) can be associated with cardiometabolic conditions. This study aimed to evaluate epicardial fat thickness (EFT), a marker of cardiometabolic disease, in SD patients.
Material and methods. In this cross-sectional and observational study, 90 patients with SD and 50 age- and sex-matched control subjects were evaluated for echocardiographic EFT and metabolic profile data.
Results. Systolic blood pressure, heart rate, high sensitive C-reactive protein, monocyte count and EFT were found to be significantly higher in the SD group (53 female; mean age, 39.3±13.3 years) compared to the control group (34 female; mean age, 39.9±13.4 years). In the multivariate logistic regression analysis, the EFT and heart rate were found to be independently associated with SD. Additionally, in the multivariate linear regression analysis including the parameters correlated with EFT and the parameters associated with EFT at the $p<0.001$ level in univariate analysis; BMI (β: 0.341, $p<0.001$) and SD disease duration (β: 0.435, $p<0.001$), as well as seborrheic dermatitis area and severity index (β: 0.177, $p=0.037$) were found to be independently associated with EFT.
Conclusions. EFT is increased in patients with SD and was also found to be independently associated with SD. Prolonged and severe SD may be a dermatological sign regarding cardiometabolic disease.

Keywords: epicardial fat thickness, seborrheic dermatitis, heart rate, systolic blood pressure, inflammation

Streszczenie

Wprowadzenie. Łojotokowe zapalenie skóry (SD) może wiązać się z chorobami kardiometabolicznymi. Niniejsze badanie miało na celu ocenę grubości nasierdziowej tkanki tłuszczowej (EFT), markera chorób kardiometabolicznych, u pacjentów z SD.
Materiały i metody. W niniejszym badaniu przekrojowym i obserwacyjnym 90 pacjentów z SD i 50 osób z grupy kontrolnej dobranych pod względem wieku i płci oceniano pod kątem echokardiograficznej EFT i danych dotyczących profilu metabolicznego.
Wyniki. Stwierdzono, że skurczowe ciśnienie krwi, częstość akcji serca, wysokoczułe białko C-reaktywne, liczba monocytów i EFT były znacząco wyższe w grupie SD (53 kobiety; średni wiek, 39,3±13,3 lat) w porównaniu z grupą kontrolną (34 kobiety; średni wiek, 39,9±13,4 lat). W wieloczynnikowej analizie regresji logistycznej stwierdzono, że EFT i częstość akcji serca były niezależnie powiązane z SD. Dodatkowo, w wieloczynnikowej analizie regresji liniowej obejmującej parametry skorelowane z EFT i parametry związane z EFT przy $p<0,001$ w analizie jednoczynnikowej; BMI (β: 0,341, $p<0,001$) i czasu trwania choroby SD (β: 0,435, $p<0,001$), a także wskaźnik powierzchni i nasilenia łojotokowego zapalenia skóry (β: 0,177, $p=0,037$) okazały się być niezależnie związane z EFT.
Wnioski. EFT jest zwiększona u pacjentów z SD i stwierdzono, że jest niezależnie powiązana z SD. Długotrwałe i ciężkie SD może stanowić objaw dermatologiczny choroby kardiometabolicznej.

Słowa kluczowe: grubość nasierdziowej tkanki tłuszczowej, łojotokowe zapalenie skóry, częstość akcji serca, skurczowe ciśnienie krwi, zapalenie

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Introduction

Seborrheic dermatitis (SD) is a common chronic-recurrent inflammatory papulosquamous skin disorder. Typical lesions involve itchy, oily and red patches of various shapes and sizes on the scalp, face and ears [1,2]. SD is frequently seen in the first three months of life, in adolescence and in young adulthood, while the incidence of the disease rises again after the age of 50 [2]. Although many theories have been suggested in the etiology, the exact etiological cause has not been proven yet [3].

Epicardial adipose tissue is located between the heart and the pericardium and, like other visceral deposits, is metabolically active and known to secrete many bioactive metabolites. The association of epicardial fat thickness (EFT) with obesity, metabolic syndrome (MetS), hypertension (HT), atrial fibrillation and atherosclerosis has consistently been shown in previous studies [4-8]. EFT can be easily measured non-invasively with transthoracic echocardiography (TTE) without radiation exposure, unlike computerized tomography [9].

It has been shown that EFT is increased in chronic inflammatory skin diseases such as psoriasis and lichen planus, and is associated with some cardiometabolic parameters in these patients [10,11]. However, no studies to date have investigated EFT in the setting of SD, despite it has been previously shown to be associated with MetS and dyslipidemia [12-14].

The aim of this study, for the first time in literature, was to investigate EFT in relation to routine and easily measurable laboratory parameters in patients with SD.

Material and methods

The study was initiated after obtaining ethics committee approval from Çanakkale Onsekiz Mart University School of Medicine (no. 2021-08). A total of 90 consecutive patients with SD and 50 age-matched healthy controls were enrolled in this case-control study conducted between November 2021 and February 2022. The exclusion criteria of the study were determined as follows: individuals under the age of 18, patients with any cardiovascular diseases (CVD), lung disease, HT, diabetes mellitus (DM), rheumatological disease, liver-kidney disorders, thyroid dysfunction, electrolyte imbalance and dyslipidemia. Additionally, morbid obese individuals with a BMI ≥35 kg/m^2 were excluded from the study.

SD was diagnosed according to clinical findings. The seborrheic dermatitis area and severity index (SDASI) was used to measure disease severity and was calculated according to the following formula [15]:

1. The area or degree of involvement of the face and scalp are independently rated on a scale of 0-6 as follows:

Degree of involvement:	Rating:
<1%	0
1-10%	1
11-20%	2
21-35%	3
36-50%	4
51-75%	5
76-100%	6

Area of Face involved (AF) _____

Area of Scalp involved (AS)_____

2. The erythema and scaling of the face and scalp are rated independently according to the following scale:
   Severity of the condition: None Very Mild Mild-Moderate Severe
   Rating: 0 1 2 3 4
   FACE: Erythema (EF) _____ Scaling (SF) _____
   SCALP: Erythema (ES) _____ Scaling (SS) _____
3. The area and severity ratings above are combined in accordance with the following formula to obtain the SASI score for the patient:
   SASI = 0.5 (AF) (EF+SF) + 0.5 (AS) (ES÷SS) SASI = _____(maximum score = 48).

Height, weight, and waist circumference measurements were performed, and body mass index (BMI) was calculated for each subject. Blood pressure was measured after minimum 15 minutes of resting, using a pressurized sphygmomanometer. The laboratory parameters of the participants (fasting glucose, triglyceride (TG), total cholesterol, high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), sedimentation and high-sensitivity C-reactive protein (hs-CRP)) were recorded.

TTE in the left lateral position was performed in all participants using VIVID 7 (GE Medical Systems, USA) according to the guidelines of the American Society of Echocardiography. Epicardial fat is identified as a hypoechoic space anteriorly to the right ventricular wall and its thickness is measured between the epicardial surface and the parietal pericardium, identified by the sliding between these two layers. EFT was measured three times by echocardiographic examination and the mean value was accepted [5].

Statistical analysis

For the data analysis, the statistical program SPSS software version 14.0 (SPSS Inc., Chicago, IL) was employed. For descriptive statistics of the data, mean, standard deviation, ratio and frequency were used. The distribution of variables was checked via Kolmogorov-Smirnov test. Comparisons between the groups were made by the use of Chi-square or Fisher's exact test for categorical variables, with independent samples t-test for normally distributed continuous variables. Mann-Whitney U test was applied when the distribution was skewed. Multivariate logistic regression analysis was performed via forward stepwise method to identify the independent determinants of SD by including the parameters that differed between the control and patient groups and those showed a significant relation to SD at the $p<0.100$ level in the univariate analysis. Pearson correlation tests were used to evaluate correlations between EFT and clinical variables. Multivariate logistic regression analysis via forward stepwise method was also performed to identify independent determinants of EFT by inclusion of parameters that showed a significant relation to EFT at the $p<0.100$ level in the univariate analysis and those correlated with EFT. Data were expressed as mean ± SD or median (min-max), minimum-maximum, and percent (%) where appropriate. Here, $p<0.05$ was considered statistically significant.

All the variables from Table 1 were examined and only those significant at $p<0.100$ level and also variables found to be significantly different between groups in Table 1, are shown in univariate analysis. Multivariate logistic regression includes all the variables in univariate analysis with a forward stepwise method.

Results

The descriptive demographical and clinical characteristics of the groups are shown in Table 1. A total of 90 patients (53 female; mean age, 39.3±13.3 years) and a control group of 50 individuals (34 female; mean age, 39.9±13.4 years) were included in this observational study. The mean SD duration was 111.33 months (range 6 to 508 months), and the mean SDASI was 14.64±4.84.

Table 1. The demographic and clinic characteristics of the study population

Characteristics	Group-1 (Seborrheic dermatitis) n=90 (64.3%)	Group-2 (Control) n=50 (35.7%)	*p*
Gender Female	53 (58.9%)	34 (68%)	*0.287*
Age (years)	39.30±13.26	39.88±13.43	*0.806*
Waist circumference (cm)	88.18±16.35	88.90±14.69	*0.790*
BMI (kg/m^2)	24.14±3.44	25.16±2.88	*0.066*
Systolic blood pressure (mmHg)	123.49±11.30	117.74±12.12	***0.007***
Diastolic blood pressure (mmHg)	73.92±5.27	73.69.±10.51	*0.893*
Heart rate (beat/minute)	83.40±11.90	75.24±10.95	***<0.001***
EF (%)	66.49±8.08	67.10±4.80	*0.576*
EFT (mm)	4.41±0.67	3.46±0.69	***<0.001***
Blood glucose (mg/dL)	96.11±24.36	103.36±30.80	*0.128*
BUN (mg/dL)	25.40±8.12	25.94±9.21	*0.729*
Creatinine (mg/dL)	0.81±0.18	0.83±0.16	*0.624*
Albumin (g/dL)	4.80±1.65	4.49±0.34	*0.099*
ALT (mg/dL)	18.00 (5-58)	20.50 (8-59)	*0.423*
AST (mg/dL)	20.00 (10-64)	25 (12-39)	***0.028***
Triglycerides (mg/dL)	103.48±52.05	116.43±40.49	*0.264*
Total cholesterol (mg/dl)	99.50 (41-794)	110 (41-208)	*0.718*
HDL-cholesterol (mg/dL)	44.01±9.22	47.00±11.93	*0.101*
LDL-cholesterol (mg/dL)	113.12±33.74	112.86±38.16	*0.967*
Hemoglobin (g/l)	13.43±2.08	13.87±1.64	*0.172*
WBC count (mcL)	7.31±1.70	7.31±1.82	*0.999*
Neutrophil count (mcL)	4.21±1.36	4.55±0.99	*0.120*
Lymphocyte count (mcL)	2.35±0.65	2.43±0.69	*0.515*
Monocyte count (mcL)	0.60 (0.20-2)	0.50 (0.20-0.90)	***0.010***
Platelet (mcL)	268.02±62.76	269.02±71.16	*0.932*
hs-CRP (mg/dL)	2.05 (0-8.60)	0.50 (0-9.8)	***<0.001***
Sedimentation (mm/h)	9 (2-49)	12 (2-22)	*0.173*

Notes: Continuous variables were presented as mean±standard deviation (SD), and categorical variables were presented as frequencies with percentages. BMI – body mass index, EF – ejection fraction, EFT – epicardial fat thickness, BUN – blood urea nitrogen, ALT – alanine aminotransferase, AST – aspartate aminotransferase, LDL – low dense lipoprotein, HDL – high dense lipoprotein, TG – triglycerides, WBC – white blood cell, hs-CRP – high sensitive C-reactive protein.

All parameters were compared between the patient and control groups, and systolic blood pressure, heart rate, hs-CRP, monocyte count and EFT were found to be significantly higher in the SD group. Albeit not considered to be clinically significant, the AST value was higher in the control group. There was no statistical difference in all other parameters between the two groups.

In the univariate analysis to determine the SD-related parameters, the SD-related parameters at the $p<0.001$ level, which are presented in Table 2, were included in the multivariate logistic regression analysis. The EFT and heart rate were found to be independently associated with SD.

Table 2. Univariate and multivariate logistic regression analyses for predicting seborrheic dermatitis

	Univariate			Multivariate		
Variables	***p***	***OR***	***(95% CI)***	***p***	***OR***	***(95% CI)***
EFT thickness	**<0.001**	8.746	4.038-18.942	**<0.001**	17.096	4.368-66.911
Heart rate	**<0.001**	1.069	1.031-1.110	**0.025**	1.084	1.010-1.163
Systolic BP	0.07	1.044	1.012-1.078	-	-	-
Albumin	0.060	4.299	0.939-19.685			
Monocyte count	**0.024**	6.193	1.265-30.321			
BMI	0.081	0.907	0.812-1.012			

Notes: CI – confidence interval, OR – odds ratio, EFT – epicardial fat thickness, BP – blood pressure, BMI – body mass index.

The parameters found to be correlated with EFT, including: SD disease duration, SDASI and others, are presented in Table 3.

Table 3. Parameters correlated with EFT in the seborrheic dermatitis group

Variables	**EFT**	
	R	***p***
Age	0.343	0.001
Male gender	0.272	0.010
BMI	0.430	**<0.001**
Waist circumference	0.392	**<0.001**
Disease duration	0.515	**<0.001**
SDASI	0.218	0.039
Total cholesterol	0.297	0.004
LDL cholesterol	0.240	0.023
hs-CRP	0.229	0.030

Notes: EFT – epicardial fat thickness, BMI – body mass index, SDASI – seborrheic dermatitis area and severity index, LDL – low dense lipoprotein, hs-CRP – high sensitive C-reactive protein.

In the multivariate linear regression analysis, including the parameters correlated with EFT and the parameters associated with EFT at the $p<0.001$ level in univariate analysis; BMI (β: 0.341, $p<0.001$), SD disease duration (β: 0.435, $p<0.001$) and SDASI (β: 0.177, $p=0.037$) were found to be independently associated with EFT (Table 4).

Table 4. Univariate and multivariate linear regression analyses for predicting EFT for seborrheic dermatitis patients

Variables	**Univariate**		**Multivariate**	
	ß	***p***	***ß***	***p***
BMI	0.187	*0.027*	0.341	**<0.001**
Disease duration	0.515	**<0.001**	0.435	**<0.001**
SDASI	0.218	0.039	0.177	0.037
Age	0.251	0.03	-	-
Waist circumference	0.277	0.01		
Total cholesterol	0.163	0.055		
LDL-cholesterol	0.171	0.045		
Triglycerides	0.171	0.044		
hs-CRP	0.229	0.030		

Notes: BMI – body mass index, SDASI – seborrheic dermatitis area and severity index, LDL – low dense lipoprotein, hs-CRP – high sensitive C-reactive protein.

Discussion

In our study, EFT, which was determined to be significantly higher in SD patients compared to the control group for the first time in the literature, was also found to be independently associated with SD. In addition, SDASI and SD disease duration were shown to be independent predictors of EFT.

EFT differs from other fat stores in the body in terms of the size, biochemical composition and metabolic activity of adipocytes. It also has significantly higher rates of lipolysis and lipogenesis compared to other visceral fat stores. Moreover, it also interacts locally with the coronary arteries and myocardium due to its anatomical proximity to the heart [16-19]. For these reasons, EFT has been evaluated in many clinical studies and has been suggested to be used as an effective biomarker for the prediction of coronary artery disease [5,6,8,20].

SD and CVD have some common pathogenic mechanisms. Both diseases are more common in males due to the effect of androgenic hormones. Androgens are known to predispose to the development of SD via increasing sebaceous gland activity. A similar mechanism may also be considered for dyslipidemia, which is a risk factor for CVD. In addition, both diseases peak in older age, are affected by stress and seasonal changes and involve vascular disorders (microangiopathy) in their pathogenesis. These attributes indicate that they have similar pathogenic mechanisms [21-23].

Furthermore, SD, like CVD, is a disease in which inflammation plays an important role in the pathogenesis. Likewise, our findings related to higher CRP and monocyte counts in the SD group may also indicate the contribution of inflammation in the pathogenesis of the disease. Lipase secreted by Malassezia is thought to activate the immune response by causing the release of free fatty acids and lipid peroxides. Moreover, several inflammatory markers, including interleukin (IL)-1α, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, tumor necrosis factor (TNF)-α, beta-defensins, interferon (IFN)-γ, nitric oxide and histamine, have been reported to be increased in SD [24-25]. In a recent study, it was reported that IL-17 may play a role in the pathogenesis of SD, similar to psoriasis [26].

The association of chronic dermatological diseases, psoriasis in particular, with MetS and its components has become of great interest in recent years. This association is considered to derive from the common chronic inflammatory nature of the diseases. EFT has an inflammation-inducing effect through the secretion of pro-inflammatory molecules such as IL-1β, IL-6, tumor necrosis factor (TNF)-α, leptin, plasminogen activator inhibitor-1 and monocyte chemoattractant protein-1 like cytokines [17-19]. In this regard, EFT is shown to be increased in psoriasis and lichen planus, compared to the control group, in recent studies [10,11]. SD is seen 2-4 times more frequently than psoriasis and lichen planus in the population [27]. Therefore, knowing the relation of SD with MetS and components, particularly the CVD, is of crucial importance in helping early diagnosis and treatment of these patients.

SD has been addressed in relation to MetS and its main components, due to its inflammatory nature, and several results have been reported [12,13,27]. Imamoglu et al., for example, noted higher rate of family history for MetS and lower HDL-C values in SD patients compared to control [12]. In another study, higher rate of MetS and higher TG levels were found in SD patients than in control [13]. In the same study, HDL-C levels were found to be significantly lower in the patient group, while systolic and diastolic blood pressure were also found to be higher in the patient group. EFT has also been reported to be independently associated with blood pressure (a known risk factor for CVD). Similarly, in our study, systolic pressure levels, as well as the heart rate, were higher in the SD patient group. An increase in systolic pressure and heart rate are findings that are associated with a poor prognosis in the course of CVD and indicate a sedentary life, however, they can be controlled through early measures.

EFT was positively correlated with advanced age, male gender, BMI, waist circumference, total cholesterol and TG values in our study. It has been previously reported that EFT is strongly associated with visceral obesity, MetS and DM [4,8,16-20]. In this context, our findings are in agreement with the literature. In addition, another important finding of our study is the demonstration of SDASI as independent predictors of EFT, the relation of which to the atherosclerosis has been previously reported.

Similarly, in studies assessing EFT in psoriasis patients, the psoriasis area severity index (PASI) has been shown to be an independent predictor of EFT [10]. In both diseases, the long course and severity of disease may be an indicator of increased inflammation, and EFT may therefore be affected more. The results of our study reveal the importance of considering EFT in long-term follow-up of SD patients, particularly in those with high SDASI or increase in SDASI over time, given the evidence on the association of EFT with subclinical atherosclerosis.

In previous studies, it has been shown that inflammatory markers such as IL-1, IL-8, and histamine return to normal with the successful treatment of SD [22,24]. Although the effect of diet on SD is not clear, it was revealed in a recent study that the severity of the disease decreased upon following a fruit-based diet, while the risk of SD increased with a traditional Western diet [28]. Interestingly, it has been reported that epicardial fat thickness can be reduced by weight loss methods such as low-calorie diet, bariatric surgery and exercise, and this decrease is more and faster than the loss of other adipose tissues in the body [29,30].

The relatively small number of patients due to its single-center design can be considered as a limitation of the study. However, since it was a prospectively designed study, this enabled the investigation of EFT and laboratory findings in SD patients during the activation period, as well as the detailed assessment of parameters such as blood pressure, BMI and waist circumference. In addition, identification of EFT (an important atherosclerosis marker) being increased in SD patients (for the first time in the literature,) seems to be a major strength of the study. However, evaluating all parameters, especially EFT, also in the remission period of the disease and comparing them with the findings of the activation period may be the subject of a new study involving SD patients.

Conclusions

SD may be a guiding dermatological sign in terms of CVD and MetS rather than a simple dermatitis. CVD is a disease that progresses insidiously and can result in sudden death [21]. In male patients with advanced age, high BMI and long term severe SD, the evaluation of CVDs that may accompany the clinical picture is of critical importance in timely recognition of atherosclerotic conditions. We should be well aware of the potential of preventable factors (cessation of sedentary life, regular physical activity, avoidance of Western type diet, weight loss, controlling blood pressure, countering stress and adherence to SD treatment) in reducing the risk of atherosclerotic diseases in these patients, as well as the intrinsically unchangeable factors (advanced age and male gender).

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