

Thickness of carotid intima and epicardial fat in rosacea: a cross-sectional study*

Asli Akin Belli¹
Ibrahim Altun³

Ilknur Altun²

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Abstract: BACKGROUND: Rosacea is a chronic facial skin disease associated with excessive inflammatory response to various triggers. Although some studies have supported the increased risk of cardiovascular diseases in rosacea, it has not been completely accepted.

OBJECTIVE: We aimed to investigate epicardial fat thickness and carotid intima-media thickness as cardiovascular risk predictors in rosacea patients.

METHODS: We conducted a cross-sectional study including 40 rosacea patients and 40 controls. Demographic data, epicardial fat thickness, carotid intima-media thickness, lipid parameters, biochemical parameters, presence of insulin resistance, and presence of metabolic syndrome of the participants were recorded.

RESULTS: Forty rosacea patients (31 female and 9 male) and 40 controls (30 female and 10 male) were enrolled in the study. Rosacea patients had significantly higher epicardial fat thickness and carotid intima-media thickness volumes than controls ($P < 0.001$). In the multivariate logistic regression analysis, epicardial fat thickness was independently related to presence of rosacea ($P < 0.001$, OR=13.31). In the multiple linear regression analysis, the epicardial fat thickness was independently associated with rosacea ($\beta = 0.47$, $P < 0.001$), carotid intima-media thickness ($\beta = 0.36$, $P < 0.001$), and systolic blood pressure ($\beta = 0.19$, $P = 0.015$) and the carotid intima-media thickness was independently associated with epicardial fat thickness ($\beta = 0.6$, $P < 0.001$). The epicardial fat thickness levels were correlated with carotid intima-media thickness ($r = 0.63$, $P < 0.001$), LDL ($r = 0.23$, $P = 0.037$), systolic blood pressure ($r = 0.45$, $P < 0.001$), and diastolic blood pressure levels ($r = 0.37$, $P = 0.001$). The carotid intima-media thickness levels were correlated with epicardial fat thickness ($r = 0.63$, $P < 0.001$), systolic blood pressure ($r = 0.04$, $P < 0.001$), and diastolic blood pressure levels ($r = 0.27$, $P = 0.016$).

STUDY LIMITATIONS: The small number of participants.

CONCLUSIONS: Examination and follow-up of rosacea patients for cardiovascular diseases may be recommended practices.

Keywords: Cardiovascular diseases; Risk factors; Rosacea

INTRODUCTION

Rosacea is a chronic facial skin disease associated with aberrant inflammatory response and vascular factors. Even though the relation of rosacea to cardiovascular diseases, as well as mortality due to cardiovascular events have been emphasized in recent studies, this relationship has not been completely accepted. Whereas Egeberg *et al.* have reported no increased risk of mortality due to cardiovascular diseases in rosacea patients, Duman *et al.* have reported high cardiovascular risk factors in rosacea patients.^{1,2} Furthermore, we have found the rate of insulin resistance increased in rosacea patients in our previous study.³

Recently, measurement of epicardial fat thickness (EFT) and carotid intima-media thickness (CIMT) have become popular to indicate the risk of cardiovascular disease and subclinical atherosclerosis as non-invasive and practical methods. It has been shown that EFT and CIMT have been increased in patients with metabolic syndrome, insulin resistance, and major cardiac events in several studies.^{4,6}

Since there is a well-known association between psoriasis and cardiometabolic risk factors, EFT and CIMT have been investigated in patients with psoriasis and these parameters have been found to be increased in some studies.^{7,9} Although a precise relationship between

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¹ Department of Dermatology, Mugla Sitki Kocman University Training and Research Hospital - Muğla, Turkey

² Department of Radiology, Mugla Sitki Kocman University Training and Research Hospital - Muğla, Turkey.

³ Department of Cardiology, Mugla Sitki Kocman University Medical School - Muğla, Turkey.

rosacea and cardiovascular diseases as in psoriasis has not been shown, rosacea has also chronic course and inflammatory pathogenesis. To the best of our knowledge, there is no study investigating EFT and CIMT in rosacea patients to predict cardiovascular events early and to assess the necessity of cardiovascular examination.

We aimed to investigate EFT and CIMT in rosacea patients compared with controls in this pilot study.

METHODS

We conducted a cross-sectional study including 40 rosacea patients and 40 age-, gender-, and body mass index (BMI)- matched controls in the Dermatology Department of Mugla Sitki Kocman University Training and Research Hospital between January 2016 and October 2016. We obtained the Ethic Committee Approval before the study. Rosacea and control groups were selected consecutively from the patients who meet the inclusion/exclusion criteria. The diagnosis of rosacea was based on the National Rosacea Society criteria. Our exclusion criteria for rosacea patients and controls were: presence of a known cardiovascular disease, diabetes mellitus, cerebrovascular disease, peripheral vascular disease, any other inflammatory disease, and pregnancy.

We recorded demographic data (age and gender), data related to rosacea (duration, subtype, and localization), smoking history, alcohol consumption, history of regular exercise, family history of cardiovascular disease (CVD), anthropometric measures, lipid parameters, fasting blood glucose (FBG), basal insulin levels, systolic blood pressure, and diastolic blood pressure levels of the participants. BMI was calculated using the formula $\text{weight (kg)} / \text{height}^2 \text{ (m}^2\text{)}$. All biochemical blood parameters were studied after a 12-hour fasting period. The homeostasis model assessment of insulin resistance (HOMA-IR) was used to calculate insulin resistance according to the following formula:

" Fasting insulin level ($\mu\text{UI}/\text{mL}$) \times Fasting blood glucose level (mg/dL) / 405". A value of > 2.7 was considered indicative of IR.

Based on the diagnostic criteria of the International Diabetes Federation (IDF-2005), waist circumference $>94\text{cm}$ in men and $>80\text{cm}$ in women, plus at least two of the following criteria: triglyceride value $>150\text{mg}/\text{dL}$ or specific treatment for this lipid abnormality, high density lipoprotein $<40\text{mg}/\text{dL}$ in men and $<50\text{mg}/\text{dL}$ in women or specific treatment for this lipid abnormality, blood pressure $\geq 130/85\text{mmHg}$ or antihypertensive treatment, fasting blood glucose $\geq 100\text{mg}/\text{dL}$ or diagnosed diabetes mellitus, were accepted as metabolic syndrome.¹⁰

A single cardiologist performed standard transthoracic echocardiography (TTE) in all patients using a Philips EPIQ 7 ultrasonography system (Koninklijke Philips N.V.; Best, The Netherlands). Epicardial fat was determined between the visceral layer of the pericardium and the outer wall of the myocardium as the relatively echo-free space. EFT was measured in end-diastole on the free wall of the right ventricle in the parasternal long- and short-axis views.¹¹ The average value of the maximal values measured at any site was considered.

A single radiologist performed carotid ultrasound in all patients by using a high-resolution B mode Doppler ultrasonography

(Aplio 500, Toshiba, Japan) with a 7.5MHz linear-array transducer. CIMT was defined as the distance between lumen-intima and the media-adventitia of the carotid arterial wall on the ultrasound. Measurements were performed at the level of the common carotid artery bulb - 1cm proximal from the bifurcation. The average value of two measurements of the right and left carotid arteries was considered.¹² Both of the cardiologist and radiologist were unaware of the participants' status (rosacea patient or control).

For the data analysis, the statistical program "SPSS for windows 22.0" was employed. For descriptive statistics of the data, we have used mean, standard deviation, ratio and frequency. The distribution of variables was checked with Kolmogorov-Smirnov test; independent samples T test and Mann-Whitney U-test were used for variables distributed normally and non-normally, respectively. The chi-square test was used for the analysis of qualitative data. Multivariate logistic regression analysis was performed with rosacea as dependent variable. In addition, multivariate linear regression analysis was performed separately with EFT and CIMT as dependent variables. Variables which showed $P < 0.1$ in univariate analysis were included in the multivariate logistic and linear regression model. Since EFT and CIMT were collinear, one of them was selected for the multiple regression analysis. Similarly, since systolic blood pressure and diastolic blood pressure were collinear, one of them was selected for the multivariate linear regression analysis. Correlation of the variables with epicardial fat thickness (EFT) and carotid intima media thickness (CIMT) was checked with Pearson correlation analysis. $P < 0.05$ was assessed as significant.

RESULTS

Forty rosacea patients (31 females, 9 males; age range 37-68 years, mean 50.35) and 40 controls (30 females, 10 males; age range 35-70 years, mean 50.52) were included in the study. The mean rosacea duration was 3.93 years (range 3 months to 20 years). Twenty-two patients (55%) had erythematotelangiectatic type and 18 patients (45%) had papulopustular type rosacea.

Rosacea patients had significantly higher EFT (Cohen's d -1.7; effect size r - 0.66; 95% CI- 0.84-1.39) and CIMT volumes (Cohen's d - 0.8; effect size r - 0.39; 95% CI- 0.05-0.15) than controls ($P < 0.001$). Additionally, the levels of systolic blood pressure and diastolic blood pressure were significantly higher than in the control group ($P < 0.05$) (Table 1).

In the multivariate logistic regression analysis, only EFT was independently related to the presence of rosacea ($P < 0.05$) (Table 2).

In the multiple linear regression analysis in which EFT was included as a dependent variable with rosacea, CIMT, LDL, and systolic blood pressure, the EFT was independently associated with rosacea, CIMT, and systolic blood pressure level ($P < 0.05$) (Table 3). In the multiple linear regression analysis in which CIMT was included as a dependent variable with rosacea, EFT, and systolic blood pressure, the CIMT was independently associated with EFT ($P < 0.001$) (Table 4).

In addition, the EFT levels were correlated with the CIMT, LDL, systolic blood pressure, and diastolic blood pressure levels ($P < 0.05$). The CIMT levels were correlated with the EFT, systolic blood pressure, and diastolic blood pressure levels ($P < 0.05$) (Table 5).

TABLE 1: Demographic, clinical, and laboratory characteristics of the participants

	Rosacea group (n=40) n (%) / mean ± SD	Control group (n=40) n (%) / mean ± SD	P
Age (years)	50.35 ± 7.59	50.52 ± 7.96	0.867
Smoking	4 (10%)	6 (15%)	0.499
Alcohol consumption	2 (5%)	2 (5%)	1
Regular exercise	16 (40%)	23 (57.5%)	0.117
Family history of CVD	5 (12.5%)	6 (15%)	0.815
EFT (mm)	4.46 ± 0.65	3.28 ± 0.59	< 0.001
CIMT (mm)	0.72 ± 0.19	0.61 ± 0.12	< 0.001
LDL (mg/dL)	133.74 ± 33.39	121.76 ± 24.68	0.058
TG (mg/dL)	141.45 ± 75.06	123.24 ± 59.11	0.177
Total Cholesterol (mg/dL)	215.54 ± 40.78	206.31 ± 30.45	0.216
HDL (mg/dL)	53.89 ± 12.31	59.87 ± 16.98	0.067
FBG (mg/dL)	95.97 ± 14.96	94.49 ± 11.46	0.791
CRP (mg/dL)	3.16 ± 3.16	2.26 ± 1.99	0.090
BMI (kg / m ²)	27.75 ± 3.08	27.14 ± 3.52	0.597
Systolic BP (mm Hg)	123.14 ± 16.94	114.36 ± 14.11	0.045
Diastolic BP (mm Hg)	80 ± 10.57	74.61 ± 6.82	0.016
HOMA-IR	2.41 ± 1.31	2.14 ± 1.19	0.329
HOMA-IR > 2.7	14 (35%)	10 (25%)	0.329
MS	13 (32.5%)	8 (20%)	0.204

Chi-square test, Independent samples t test, and Mann-Whitney U-test. SD- Standard deviation; CVD- Cardiovascular disease; EFT- Epicardial fat thickness; CIMT- Carotid intima-media thickness; TG-Triglyceride; FBG- Fasting blood glucose; BMI- Body mass index; BP- Blood pressure; HOMA-IR- Homeostasis model assessment of insulin resistance; MS- Metabolic syndrome.

TABLE 2: Prediction of presence of rosacea in the study population by multiple logistic regression analysis

Variables	Univariate analysis P	Odds Ratio (95% CI)	Multivariate analysis β P	Odds Ratio (95% CI)
Gender	0.793	1.15 (0.41-3.22)		
Age	0.865	1.01 (0.95-1.06)		
Smoking	0.502	1.59 (0.41-6.12)		
Alcohol consumption	1	1 (0.13-7.47)		
Regular exercise	0.119	2.03 (0.83-4.95)		
Family history of CVD	0.815	0.86 (0.24-3.09)		
Waist circumference	0.911	1.01 (0.957-1.05)		
EFT	< 0.001	12.87 (4.43-37.36)	2.59 < 0.001	13.31 (4.15-42.68)
LDL	0.062	1.02 (0.99-1.03)	0.01 0.534	1.01 (0.98-1.03)
TG	0.180	1.01 (0.99-1.01)		
Total cholesterol	0.215	1.01 (0.99-1.02)		
HDL	0.073	0.97 (0.94-1.01)	-0.05 0.087	0.96 (0.91-1.01)
FBG	0.413	1.01 (0.98-1.05)		
CRP	0.124	1.18 (0.95-1.46)		
Diastolic BP	0.014	1.08 (1.02-1.15)	0.05 0.291	1.05 (0.96-1.15)
BMI	0.592	1.04 (0.91-1.19)		
IR	0.331	1.61 (0.61-4.25)		
MS	0.207	1.93 (0.69-5.34)		

CI- Confidence interval; CVD- Cardiovascular disease; EFT- Epicardial fat thickness; TG-Triglyceride; FBG- Fasting blood glucose; CRP- C-reactive protein; BP- Blood pressure; BMI- Body mass index; IR- Insulin resistance; MS- Metabolic syndrome.

TABLE 3: Independent predictors for epicardial fat thickness by multivariate linear regression analysis

Variables	Univariate analysis P	Multivariate analysis β P
Rosacea	< 0.001	0.47 < 0.001
Gender	0.564	
Age	0.199	
Duration of rosacea	0.458	
Subtype of rosacea	0.763	
Smoking	0.267	
Alcohol consumption	0.75	
Regular exercise	0.427	
Family history of CVD	0.572	
Waist circumference	0.285	
CIMT	< 0.001	0.36 < 0.001
LDL	0.037	0.06 0.388
TG	0.971	
Total cholesterol	0.118	
HDL	0.742	
FBG	0.697	
CRP	0.824	
Systolic BP	< 0.001	0.19 0.015
BMI	0.814	
IR	0.448	
MS	0.908	

CIMT- Carotid intima media thickness; CVD- Cardiovascular disease; TG-Triglyceride; FBG- Fasting blood glucose; CRP- C-reactive protein; BP- Blood pressure; BMI- Body mass index; IR- Insulin resistance; MS- Metabolic syndrome.

TABLE 4: Independent predictors for carotid intima-media thickness by multivariate linear regression analysis

Variables	Univariate analysis P	Multivariate analysis β P
Rosacea	<0.001	-0.03 0.814
Gender	0.261	
Age	0.197	
Duration of rosacea	0.579	
Subtype of rosacea	0.984	
Smoking	0.859	
Alcohol consumption	0.898	
Regular exercise	0.936	
Family history of CVD	0.519	
Waist circumference	0.724	
EFT	< 0.001	0.6 < 0.001
LDL	0.273	
TG	0.601	
Total cholesterol	0.258	
HDL	0.969	
FBG	0.321	
CRP	0.967	
Systolic BP	0.001	0.11 0.276
BMI	0.748	
IR	0.289	
MS	0.119	

CVD- Cardiovascular disease; EFT- Epicardial fat thickness; TG-Triglyceride; FBG- Fasting blood glucose; CRP- C-reactive protein; BP- Blood pressure; BMI- Body mass index; IR- Insulin resistance; MS- Metabolic syndrome.

TABLE 5: Correlation of the variables with epicardial fat thickness (EFT) and carotid intima-media thickness (CIMT)

Variables	EFT CC P	CIMT CC P
Age	0.145 0.199	0.146 0.197
Waist circumference	0.123 0.285	0.041 0.724
EFT	1	0.629 <0.001
CIMT	0.629 <0.001	1
LDL	0.234 0.037	0.124 0.273
TG	-0.004 0.971	0.059 0.601
Total cholesterol	0.176 0.118	0.128 0.258
HDL	-0.037 0.742	0.004 0.969
FBG	0.044 0.697	0.112 0.321
CRP	0.026 0.824	-0.005 0.967
Systolic BP	0.447 <0.001	0.371 <0.001
Diastolic BP	0.369 0.001	0.272 0.016
BMI	0.027 0.814	-0.037 0.748
HOMA-IR	0.062 0.583	0.052 0.647

EFT- Epicardial fat thickness; CIMT- Carotid intima media thickness; CC- Correlation coefficient; TG-Triglyceride; FBG- Fasting blood glucose; CRP- C-reactive protein; BP- Blood pressure; BMI- Body mass index; HOMA-IR- Homeostasis model assessment of insulin resistance.

DISCUSSION

Rosacea is a common cutaneous disease with the frequent involvement of cheek, nose, forehead, and chin. Although it is known to be a chronic inflammatory disease, ambiguity associated with the pathogenesis is still continuing. Whereas the relation of rosacea to cardiovascular diseases has been emphasized in recent years, some new studies have reported no association between these diseases. The diverse results have encouraged us to conduct this pilot study. We found the volumes of EFT and CIMT increased in rosacea patients when compared to controls.

Epicardial fat tissue, a type of visceral adipose tissue, surrounds the coronary vessels and heart, particularly atrioventricular and interventricular grooves. Evaluation of EFT and CIMT have been stated to show cardiac adiposity and subclinical atherosclerosis, respectively. EFT acts as an endocrine organ and can induce coronary artery disease by secreting various proinflammatory cytokines, chemokines, and hormones including tumor necrosis factor- α (TNF- α), plasminogen activator inhibitor-1, IL-6, monocyte chemoattractant protein-1 (MCP-1), and leptin. Thus, measurement of EFT and CIMT has been proposed as a new predictor of cardiometabolic diseases. In various studies, EFT and CIMT have been found increased in the patients with insulin resistance, major cardiac events, complex coronary artery disease, acute ischemic stroke,

and diabetes mellitus.^{4,6,13-15} Moreover, Hwang *et al* reported that EFT is related to the formation of non-calcified coronary plaque in asymptomatic individuals.¹⁶ Similarly, it has been stated that EFT is associated with atherosclerotic plaque and CIMT by Kocaman *et al*.¹⁷ In our study, EFT and CIMT were also strongly correlated.

In the pathogenesis of rosacea, increased inflammatory response to various triggers associated with cathelicidin peptides and endoplasmic reticulum stress have been demonstrated. Pro-inflammatory cytokines such as IL-8, IL-1 β , and TNF- α and inflammasome-related genes have been found overexpressed in the facial skin of rosacea patients.¹⁸⁻²⁰ Firstly, the relation of rosacea to cardiovascular diseases have been investigated by Duman *et al.* and cardiovascular risk factors have been found increased in rosacea patients.² In another study, dyslipidemia and hypertension have been reported increased in rosacea patients.²¹ Another study reported that rosacea patients had more dyslipidemia and hypertension than patients without rosacea. Rainer *et al.* have noted that the risk of cardiovascular diseases, metabolic diseases, and gastroesophageal reflux disease are increased in the patients with moderate-severe rosacea than in the patients with mild rosacea.²² In our previous study, the rate of insulin resistance and levels of FBG, total cholesterol, systolic blood pressure, and diastolic blood pressure were significantly higher in rosacea patients than in controls.³ However, Egeberg *et al.* have reported no increased risk of mortality due to cardiovascular events in rosacea patients in their two studies.^{1,23} These conflicting results encouraged us to deepen this topic. In the current study, EFT and CIMT levels were significantly higher in rosacea patients than in controls. Additionally, the other cardiovascular risk factors including systolic blood pressure and diastolic blood pressure levels were significantly higher in the rosacea group than in the control group. The current results may be explained by that decreased activity of paraoxone-1 (PON1), an antioxidant enzyme, increased

cathelicidin gene expression; similar pro-inflammatory pathways have been shown in atherosclerosis and cardiovascular diseases.²⁴⁻²⁷

Among the other chronic cutaneous inflammatory diseases, EFT and CIMT have been evaluated in psoriasis patients in a few studies. Torres *et al.* have compared EFT, abdominal visceral fat, and coronary artery calcification in 100 psoriasis patients and 202 controls and found significantly increased EFT volume and subclinical atherosclerosis in psoriasis patients.⁷ In another study, Bacaksız *et al.* have reported that EFT was significantly increased in psoriasis patients, particularly with severe disease.⁸ Bulbul Sen *et al.* have found EFT and CIMT levels increased in 65 psoriasis patients compared to 50 controls and have noticed that EFT could be a practical marker to indicate subclinical atherosclerosis and high cardiovascular risk in psoriasis patients.⁹ Although there is no precise relationship between rosacea and cardiovascular diseases as in psoriasis, rosacea is also a chronic inflammatory disease.

To exclude the bias due to obesity, we enrolled age-, gender, and also BMI-matched individuals in both groups. However, our limitations were the small number of the participants in each group and use of trans-thoracic echocardiography to measure EFT rather than magnetic resonance imaging (MRI), which is the gold standard for the measurement of EFT.

CONCLUSION

In conclusion, the volumes of EFT and CIMT were significantly higher in the rosacea group than in the control group and strongly correlated with each other. According to the current results and some previous studies, examination and follow-up of rosacea patients for developing cardiovascular diseases with biochemical tests and cardiology consultation may be recommended clinical practices. However, our results should be confirmed with a larger number of patients in future studies. □

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MAILING ADDRESS:

Asli Akin Belli, MD

Mugla Sitki Kocman University, Training and Research Hospital, Department of Dermatology
48000 Mugla, Turkey.

E-mail: dr_asliakin@hotmail.com

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