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. Furthermore, we have found the rate of insulin resistance increased in rosacea patients in our previous study. 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. 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. Although a precise relationship between

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

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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 (β=0.47, P<0.001), carotid intima-media thickness (β=0.36, P<0.001), and systolic blood pressure (β=0.19, P=0.015) and the carotid intima-media thickness was independently associated with epicardial fat thickness (β=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
rosacea and cardiovascular diseases as in psoriasis has not been shown, rosacea has also chronic course and inflammatory pathogene-
sis. 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 Sıtkı Kocman
University Training and Research Hospital between January 2016
and October 2016. We obtained the Ethic Committee Approval be-
fore the study. Rosacea and control groups were selected consecu-
tively from the patients who meet the inclusion/exclusion criteria.
The diagnosis of rosacea was based on the National Rosacea Soci-
ety criteria. Our exclusion criteria for rosacea patients and controls
were: presence of a known cardiovascular disease, diabetes melli-
tus, 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 weight (kg) /
height² (m²). All biochemical blood parameters were studied after
a 12-hour fasting period. The homeostasis model assessment of in-
sulin resistance (HOMA-IR) was used to calculate insulin resistance
according to the following formula:

\[
\text{HOMA-IR} = \frac{\text{Fasting glucose (mg/dL)} \times \text{Fasting insulin (µU/mL)}}{405}
\]

A value of > 2.7 was considered indicative of IR.

Based on the diagnostic criteria of the International Di-
abetes Federation (IDF-2005), waist circumference >94cm in men
and >80 cm in women, plus at least two of the following criteria:
triglyceride value >150 mg/dL or specific treatment for this lipid
abnormality, high density lipoprotein <40mg/dL in men and <50
mg/dL in women or specific treatment for this lipid abnormality,
blood pressure ≥130/85 mmHg or antihypertensive treatment, fast-
ing blood glucose ≥100mg/dL or diagnosed diabetes mellitus, were
accepted as metabolic syndrome.²⁰

A single cardiologist performed standard transthoracic echocardiography (TTE) in all patients using a Philips EPIQ 7 ul-
trasonography system (Koninklijke Philips N.V.; Best, The Nether-
lands). Epicardial fat was determined between the visceral layer of
the pericardium and the outer wall of the myocardium as the rel-
atively 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 pa-
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. Mea-
surements were performed at the level of the common carotid artery
bulbus - 1cm proximal from the bifurcation. The average value of
two measurements of the right and left carotid arteries was consid-
ered.²² 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 win-
dows 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
and Anderson-Darling test; independent samples T test and Mann-Whitney U-test were
used for variables distributed normally and non-normally, respec-
tively. 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 re-
gression 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 regres-
sion 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 ro-
sacea duration was 3.93 years (range 3 months to 20 years). Twenty-
two patients (55%) had erythematotelangiectatic type and 18 pa-
tients (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 (Co-
hen’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 di-
astolic 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 in-
cluded 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 multi-
ple linear regression analysis in which CIMT was included as a depen-
dent 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).

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### Table 1: Demographic, clinical, and laboratory characteristics of the participants

|                                | Rosacea group (n=40) | Control group (n=40) | 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%)               | 0.117 |
| **Regular exercise**           | 16 (40%)             | 23 (57.5%)           |     |
| **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/m²)**                | 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 | 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.

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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. Moreover, Hwang et al reported that EFT is related to the formation of non-calcified coronary plaque in asymptomatic individuals. Similarly, it has been stated that EFT is associated with atherosclerotic plaque and CIMT by Kocaman et al. 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-1β, and TNF-α and inflammasome-related genes have been found overexpressed in the facial skin of rosacea patients. 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. In another study, dyslipidemia and hypertension have been reported increased in rosacea patients. 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. 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. However, Egeberg et al. have reported no increased risk of mortality due to cardiovascular events in rosacea patients in their two studies. 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.

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. In another study, Bacaksız et al. have reported that EFT was significantly increased in psoriasis patients, particularly with severe disease. 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. 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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