

ORIGINAL ARTICLE

Evaluation of subclinical atherosclerosis in rosacea patients by flow-mediated dilatation method

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Abstract

Background: Rosacea may contribute to the development of cardiovascular (CV) diseases by causing endothelial dysfunction (ED), which is known to be the initial step of atherosclerosis, due to its inflammatory features.

Objective: This study aimed to assess ED in rosacea patients using the flow-mediated dilatation (=dilation) (FMD) method.

Methods: Seventy-three rosacea patients and 73 age, gender-matched healthy volunteers were enrolled. Individuals with cardiac risk factors, pregnant, and lactating women were excluded. Demographic, clinical data and anthropometric measurements were recorded. FMD measurement was performed ultrasonographically by a cardiologist. Systolic and diastolic blood pressures (BP) were measured and hemogram, erythrocyte sedimentation rate (ESR), C-Reactive Protein (CRP), total cholesterol, triglyceride, low-density lipoprotein (LDL), high-density lipoprotein (HDL), neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), mean platelet volume (MPV), and fasting blood glucose values were assessed.

Results: The FMD value was statistically lower in rosacea patients compared with healthy controls ($p = 0.000$). Metabolic syndrome, systolic and diastolic BPs, and plasma NLR were higher in the rosacea group ($p = 0.009$, $p = 0.000$, $p = 0.000$, $p = 0.000$, respectively). According to the multivariate linear regression analysis, rosacea type significantly predicted FMD.

Conclusions: Rosacea is not only a disease limited to the skin, but it may also have systemic involvement. A significant difference was found between FMD values measured in between the case and control groups, suggesting rosacea may have an atherogenic effect. Possible cardiac risks should be considered in rosacea patients, and further evaluation could be warranted.

KEYWORDS

atherosclerosis, endothelium, flow mediated dilation, neutrophil lymphocyte ratio, rosacea

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1 | INTRODUCTION

Rosacea is a chronic, inflammatory skin dermatosis that affects mainly midline of the face. It is characterized by erythema, telangiectasia, papules, pustules, and may result in fibrosis and deformities. Although the pathogenesis of this disease has not been fully explained, it has been suggested that immune factors, ultraviolet (UV) rays, microorganisms, neurovascular disorders, environmental and genetic factors may play a role.^{1,2}

Rosacea may occur concomitantly with various systemic diseases such as metabolic syndrome, inflammatory bowel diseases, multiple sclerosis, Parkinson's Disease, and migraine.² The relationship between rosacea and cardiovascular CV diseases has been evaluated by various researchers who found conflicting relationships. Some studies detected an increase in CV risk in rosacea patients, whereas an enhanced risk was not found in others. In a recent systematic review, CV diseases such as coronary artery diseases, metabolic syndrome, and hypertension were found to be significantly associated with rosacea.³

Endothelial dysfunction (ED) is known to be the first step in atherosclerotic diseases.⁴ Since its introduction in 1989, the flow-mediated dilatation (FMD) test has served well as an ultrasonographic, non-invasive, and inexpensive method for demonstrating subclinical atherosclerosis.⁵ Its major negative feature is that it is an operator-dependent assessment. A higher percentage of FMD indicates a healthy endothelial function, while low values indicate ED. ED may be detected before prominent atherosclerosis and other coronary diseases occur, making FMD a reliable early-stage predictor of CV events.⁶ FMD studies have evaluated inflammatory diseases of the skin such as psoriasis⁷ but, as far as we know, there is no study examining FMD in rosacea patients.

The primary objective of our study is to demonstrate whether there is subclinical atherosclerosis in rosacea patients by using the FMD method. The secondary objectives are to compare the inflammation indicators (C-reactive protein [CRP], erythrocyte sedimentation rate [ESR], mean platelet volume [MPV], neutrophil/lymphocyte [NLR], and platelet/lymphocyte ratios [PLR]) between rosacea patients and control group, to evaluate whether there is a significant correlation between the above inflammation indicators and FMD values, and assess the relationship between rosacea and metabolic syndrome.

2 | MATERIALS AND METHOD

2.1 | Study design

The study was an observational, case-controlled study conducted in Dermatology and Cardiology Clinics between April 15, 2021, and May 31, 2021. The rosacea group consisted of 73 individuals clinically diagnosed with rosacea and the control group ($n = 73$) was recruited from healthy volunteers who applied to Cardiology Outpatient Clinic for routine control. All participants were between

the ages of 18–65 and met the inclusion criteria. Written and informed consent was obtained from all participants.

Exclusion criteria of the study were (1) hypertensive disease; (2) diabetes mellitus (DM); (3) previous cerebrovascular disease; (4) coronary artery disease (CAD); (5) chronic renal or liver failure; (6) chronic systemic steroid use within past three months; (7) use of oral contraceptives or hormone replacement treatment; (8) pregnancy; (9) lactation; (10) alcohol abuse; (11) antihypertensive or antiaggregant drug use; (12) documented history of metabolic syndrome.

Inclusion criteria were being between the ages of 18–60, volunteering to participate in the study and signing the written consent form and receiving a clinical diagnosis of rosacea by a dermatologist for the case group.

Fitzpatrick skin type, age-onset, duration of rosacea, localization, and severity were recorded. The types of rosacea were documented as erythematotelangiectatic (ET), papulopustular (PP), phymatous, and ocular rosacea. Patients having only ocular rosacea were excluded from the study. Patients suffering only ocular rosacea were excluded from the study. Smoking, alcohol consumption, exercise habits, factors that trigger rosacea, family history of rosacea and history of cardiac disease were also noted. Height, weight, waist, and hip circumferences of all participants were measured and recorded.

The study was conducted in accordance with the Declaration of Helsinki and good clinical practice.

2.2 | Laboratory work-up

Fasting blood glucose, hemogram, ESR, CRP, total cholesterol, triglyceride, HDL, and LDL tests of all the participants were studied from peripheral venous blood taken after eight hours of fasting.

2.3 | Measurement of arterial blood pressure

The systolic and diastolic BPs were measured manually at rest from the left brachial artery.

2.4 | Assessment of flow-mediated dilation

Measurements were performed by a single cardiologist using General Electric Vivid 3 echocardiography device and General Electric 10 L linear probe.

The FMD was assessed in the supine position after 8 h of fasting. None of the patients had consumed caffeinated beverages or alcohol 12h before. Neither had they smoked in that interim. The patients did not exercise 12h before the examination, and rested for 10–15 min before the procedure. The examination room temperature was maintained at an optimal 22–23°C. The right brachial artery was used for FMD measurement, and it was palpated medial to the antecubital fossa before the ultrasound probe was placed on the artery on the skin. Arterial trace was detected by placing the

probe on the artery in the longitudinal section. A straight segment, where the artery did not show tortuosity, was found and the image was recorded. Then, the arterial diameter was measured from tunica intima to tunica intima. This process was repeated three times, and the mean value was calculated. This obtained value was recorded as the basal diameter (BD) of the brachial artery.

After the BD was taken, the cuff was placed on the patient's ipsilateral forearm and locked by increasing the systolic BP value measured at baseline by 50 mmHg. The cuff was left on the arm for five minutes. One minute after the cuff was deflated, the post-flow diameter (PFD) of the artery was measured three times with above-mentioned method, and the mean value was obtained. FMD values were calculated with the equation $FMD = (PFD / BD) \times 100$ as a percentage expression of the ratio of basal diameter to endothelium-dependent vasodilator response.

2.5 | Statistical analysis

Data obtained were analyzed with IBM SPSS (Statistical Package for the Social Sciences) 22.0 program. Descriptive statistics were expressed as mean and standard deviation for normally distributed numerical data, as median and minimum-maximum value (min-max) for non-normally distributed data, and as numbers and percentages for nominal data. Mann-Whitney U test, and independent sample t-test were used for the analysis of independent quantitative data. Chi-square test and Fisher's exact test were used for the analysis of qualitative data. Linear regression analysis was performed to determine whether statistically significant values affected endothelial function independently. In statistical analyses in the study, *p* values below 0.05 were considered as statistically significant.

TABLE 1 Clinical features of rosacea patients

		Case Group		
		Mean. ± SD/n-%		Median
Age-onset of the disease		32.5	± 10.2	35.0
Disease Duration (years)		8.1	± 6.9	6.0
Rosacea type	Erythematotelangiectatic	37	50.7%	
	Papulopustular	33	45.2%	
	Phymatous	3	4.1%	
Disease severity	Mild	24	32.9%	
	Moderate	37	50.7%	
	Severe	12	16.4%	
Family history of rosacea		23	31.5%	
Eye involvement		17	23.3%	
Lesion localization	Central face	59	80.8%	
	Malar region	72	98.6%	
	Chin	17	23.3%	
	Forehead	26	35.6%	
	Whole face	8	11.0%	

Abbreviation: SD, standard deviation.

3 | RESULTS

3.1 | Demographics and clinical data

Among rosacea patients, 64.4% (*n* = 47.0) were female, and 65.8% (*n* = 48.0) of the control group were female. The mean age of the rosacea group was 39.8 ± 8.7 years (median = 41.0 years); the control group's mean age was 38.4 ± 8.0 years (median = 38.0 years). There was no significant difference between the two groups in terms of age, gender, Fitzpatrick skin type, premature CV (≤ 45 years), and CV disease history, smoking habit, and smoking quantity (pack/year) (*p* > 0.005).

The presence of metabolic syndrome was found to be significantly higher in the case group (*p* = 0.009). The age of onset of rosacea was 32.5 ± 10.2 years (median = 35.0 years), and the mean disease duration was 8.1 ± 6.9 years (median = 6.0 years). Among patients, 31.5% of the patients had a family history of rosacea. 50.7% (*n* = 37) of patients had ET-type rosacea, followed by the PP (45.2%), and the phymatous type (4.1%). The disease severity was moderate in 50.7%, mild in 32.9%, and severe in 16.4% of patients. Cheek localization was observed in 98.6% of patients, followed by central face (nose) (80.8%). (Table 1). 23.3% of them had eye involvement. The most common triggering factors were temperature (89%), UV light (82.2%), and spicy foods (72.6%). It was observed that 100% of the patients received topical metronidazole treatment (Table 2).

3.2 | Outcomes of laboratory tests and measurement of FMD

The participants were divided into two groups according to their FMD scores: <10% and >10%. Eighty-six per cent (*n* = 55) of the

TABLE 2 Triggering factors and previous treatment status in patients with rosacea

		Case Group	
		n	%
Triggering factors	Stress	52	71.2%
	UV light	60	82.2%
	Heat	65	89.0%
	Cold	26	35.6%
	Wind	33	45.2%
	Hot beverages	14	19.2%
	Caffeine	13	17.8%
	Physical exercise	18	24.7%
	Spicy food	53	72.6%
Previous treatment status	Topical metronidazole	73	100.0%
	Topical sodium sulfacetamide	14	19.2%
	Topical benzoyl peroxide	8	11.0%
	Topical permethrin	30	41.1%
	Topical antibiotics	18	24.7%
	Topical ivermectin	2	2.7%
	Topical azelaic acid	14	19.2%
	Topical calcineurin inhibitors	8	11.0%
	Topical retinoids	5	6.8%
	Oral isotretinoin	4	5.5%
	Oral azithromycin	10	13.7%
	Oral doxycycline	8	11.0%
	Oral tetracycline	4	5.5%
	Laser applications	6	8.2%

group with an FMD score below 10% consisted of rosacea patients. The number of patients with rosacea was significantly higher in the group with FMD < 10% compared to the group with FMD > 10% ($p = 0.000$). ET and PP rosacea types were significantly higher in the group with FMD scores < 10% ($p = 0.008$, $p = 0.024$, respectively). There was no significant difference between the two groups with regard to the incidence of phymatous rosacea ($p > 0.005$). Systolic and diastolic BPs were significantly higher in the group with FMD < 10%. ($p = 0.000$, $p = 0.033$, respectively) (Table 3).

There was no significant difference between the groups in terms of PLR, glucose, CRP, ESH, total cholesterol, LDL, HDL, and triglyceride levels ($p > 0.005$). NLR was significantly higher in the group having FMD score of < 10% compared to the group with an FMD score of > 10% ($p = 0.032$) (Table 4).

3.3 | Comparison of demographic, clinical, and laboratory data by rosacea disease severity

Patients were divided into two groups—mild and moderate–severe—according to disease severity. There was no significant difference between the two groups in terms of age, gender, PP and phymatous

type rosacea, eye involvement, family history of rosacea, presence of metabolic syndrome, FMD score, PLR, systolic and diastolic BPs ($p > 0.005$). ET rosacea was significantly higher in the mild disease group ($p = 0.016$). The rate of forehead localization was significantly higher in the moderate–severe group ($p = 0.018$). Previous topical sodium sulfacetamide and permethrin treatment were significantly higher in the moderate–severe group compared with the mild group (respectively, $p = 0.027$, $p = 0.001$). NLR levels were statistically elevated in the moderate–severe group compared with the mild group ($p = 0.016$) (Table 5).

3.4 | Relationship between clinical and laboratory data of rosacea types

The patients were examined in two groups as ET and PP rosacea. According to the comparison of clinical and laboratory data, no significant difference was found between the two rosacea types in terms of pre- and post-brachial diameters, systolic BP, NLR and PLR, glucose, ESR, total cholesterol, LDL, HDL, and triglyceride levels ($p > 0.005$). FMD was significantly lower in PP patients compared with ET patients ($p = 0.038$). Diastolic BP, MPV, and CRP levels were significantly higher in the PP group compared with ET patients ($p = 0.017$, $p = 0.028$, $p = 0.010$, respectively) (Table 6).

3.5 | The relationship of disease duration with FMD, BP and laboratory values

There was no significant correlation between disease duration and FMD, NLR, PLR MPV, glucose, CRP, ESH, total cholesterol, LDL, HDL, triglyceride, systolic and diastolic BPs ($p > 0.005$) (Table 7).

3.6 | Linear regression analysis

A single-factor analysis of variance was performed on independent groups to determine a possible association of rosacea disease with ED. Possible related parameters: family history of rosacea, type of rosacea, systolic BP, previously administered azithromycin, and permethrin treatments. These parameters were included in the equation for linear regression analysis to understand their relationship with FMD. Rosacea type significantly predicted the FMD score. [Beta = 0.25 t (66) = 2.12 $p = 0.038$, $pr = 2 0.064$] (Table 8).

4 | DISCUSSION

Rosacea is a chronic, inflammatory skin disease that affects mainly the midline of the face. Although the etiopathogenesis of the disease has not been fully elucidated, many theories are currently contemplated.⁸

TABLE 3 Comparison of group, demographic, and clinical data according to FMD rate

		FMD (<10%)		FMD (>10%)		p
		Mean. ± SD/n-%	Median	Mean ± SD/n-%	Median	
Group	Case	55	85.9%	18	22%	0.000 ^b
	Control	9	14.1%	64	78%	
Gender	Female	40	62.5%	55	67.1%	0.565 ^b
	Male	24	37.5%	17	32.9%	
Age		39.3 ± 8.8	40.0	39.0 ± 8.1	39.5	0.757 ^a
Rosacea type	Erythematotelangiectatic	23	35.9%	14	17.1%	0.008 ^b
	Papulopustular	29	45.3%	4	4.9%	0.024 ^b
	Phymatous	3	4.7%	0	0.0%	0.570 ^c
Eye involvement		11	64.7%	6	35.2%	0.335 ^b
Metabolic syndrome		9	14.1%	4	4.9%	0.053 ^c
Systolic BP (mmHg)		124.4 ± 6.4	125.0	120.0 ± 6.0	120.0	0.000 ^a
Diastolic BP (mmHg)		77.8 ± 7.1	75.0	75.1 ± 6.5	75.0	0.033 ^a

Abbreviations: FMD, flow-mediated dilation; SD, standard deviation.

^aMann-Whitney U test.

^bChi-square test.

^cFisher's Exact test.

The results showing that endothelial dysfunction is more prominent in ET and PP type of rosacea ($p < 0.05$).

TABLE 4 Comparison of laboratory data by FMD rate

	FMD (<10%)		FMD (>10%)		p
	Mean. ± SD/n-%	Median	Mean. ± SD/n-%	Median	
NLR	2.1 ± 0.8	1.9	1.8 ± 0.6	1.7	0.032
PLR	126.3 ± 42.3	117.9	116.2 ± 32.1	111.0	0.243
MPV (fl)	9.9 ± 0.9	9.9	10.3 ± 1.0	10.1	0.019
Glucose (mg/dl)	96.4 ± 8.9	96.0	95.9 ± 11.5	97.0	0.981
CRP (mg/L)	1.7 ± 2.2	1.1	1.7 ± 1.4	1.2	0.430
ESR (mm/hour)	7.8 ± 8.9	4.5	9.2 ± 12.7	4.0	0.966
Total Cholesterol (mg/dl)	192.1 ± 38.8	193.0	188.5 ± 31.8	183.0	0.516
LDL (mg/dl)	117.8 ± 33.1	111.0	114.3 ± 26.7	113.0	0.773
HDL (mg/dl)	50.3 ± 13.3	48.5	50.7 ± 12.4	4.5	0.699
Triglyceride (mg/dl)	123.3 ± 77.8	100.5	119.8 ± 76.1	98.5	0.818

Mann-Whitney U test

NLR value is higher in the individuals having FMD value of <10% ($p < 0.05$). MPV value was lower in individuals having FMD value of <10% ($p > 0.05$).

The vascular endothelium covers all the vessels within the body and is a dynamic organ that is considered hormonally active. ED, which can be detected long before the appearance of clinically detectable atherosclerosis, is the earliest stage of the atherosclerosis process, and endothelial function primarily improves before regression of atherosclerosis. Due to the inflammatory properties of rosacea, it has been posited that it may contribute to the formation of cardiovascular disease by causing ED.⁹

Vascular measurement methods such as FMD and/or biochemical tests may be used to assess ED. One of the non-invasive methods used to evaluate endothelial function is FMD. In many studies, it has been reported that FMD value measured from the brachial

artery is a prognostic marker in cardiovascular diseases.¹⁰ The cutoff value of FMD measured from the brachial artery was determined as 10% by Celermajer.¹¹ However, although this value is not accepted as a universal value, it can be concluded that as FMD decreases, ED increases.¹² There are different results for FMD response in different studies. While some studies have reported that the dilatation response in healthy adults should be between 10% and 20%,¹³ this rate has been given as 5–10% in other studies.¹⁴ The data of a study reported that if the FMD value measured from the brachial artery is below 10%, it has a highly predictive degree for ischemia.¹⁵ Therefore, the cutoff value for FMD was taken as 10% in our study in the light of this data. Thus, the values below 10% of FMD were

TABLE 5 Comparison of demographic, clinical, and laboratory data by rosacea disease severity

		Mild			Moderate–Severe			p
		Mean. ± SD/n-%		Median	Mean. ± SD/n-%		Median	
Gender	Female	14		58.3%	33		67.3%	0.450 ^b
	Male	10		41.7%	16		32.7%	
Age		38.3	± 8.4	40.0	40.6	± 8.9	42.0	0.169 ^a
Rosacea type	Erythematotelangiectatic	17		70.8%	20		40.8%	0.016 ^b
	Papulopustular	7		29.2%	26		53.1%	0.054 ^b
	Phymatous	0		0%	3		6.1%	0.546 ^c
Lesion localization-forehead		4		16.6%	22		44.8%	0.018 ^c
Eye involvement		5		20.8%	12		24.4%	0.728 ^b
Family history of rosacea		10		41.6%	13		26.5%	0.191 ^b
Metabolic syndrome		4		16.7%	7		14.3%	1.000 ^c
Previous treatment- Sodium sulfacetamide		1		4.1%	13		26.5%	0.027 ^c
Previous treatment- Permethrin		3		12.5%	27		55.1%	0.001 ^c
FMD (%)		11.6	± 5.8	9.5	9.6	± 4.5	9.0	0.087 ^a
NLR		1.8	± 0.5	1.6	2.3	± 0.9	2.1	0.016 ^a
PLR		114.7	± 29.7	110.9	133.4	± 44.2	129.7	0.056 ^a
Systolic BP (mmHg)		123.5	± 5.4	125.0	125.0	± 6.9	125.0	0.234 ^a
Diastolic BP (mmHg)		77.2	± 6.4	77.5	79.1	± 6.9	80.0	0.243 ^a

Abbreviation: BP, blood pressure; FMD, flow-mediated dilation; NLR, neutrophile/lymphocyte ratio; PLR, platelet/lymphocyte ratio; SD, standard deviation.

^aMann–Whitney U test.

^bChi-square test.

^cFisher's Exact test.

The rosacea disease is more severe in PP type of patients. The forehead localization is more frequent in severe rosacea patients. Permethrin use is more common in patients having severe disease compared to mild disease. NLR value is higher in moderate-severe rosacea patients compared to mild group ($p < 0.05$ for all).

accepted as ED. FMD ratio was divided as below 10% and above 10%, the NLR in the group with FMD < 10% was found to be statistically significantly higher than the group with FMD > 10%. This can be interpreted that FMD may be an indicator of inflammatory status in patients with rosacea.

The results of studies evaluating the relationship between rosacea and cardiovascular diseases are variable. In a study conducted by Egeberg et al., it was reported that rosacea was not associated with increased cardiovascular risk, but weakly associated with elevated risk of myocardial infarction.¹⁶ In another study, CRP, total cholesterol, and LDL values were found to be higher in rosacea patients than in healthy controls. This findings also suggests that rosacea may be associated with cardiovascular diseases.⁴ Coronary artery disease, hypertension, and dyslipidemia were reported to be statistically associated with rosacea in a case–controlled study.¹⁷ When the relationship between rosacea and metabolic syndrome was examined, a positive correlation was found in some studies, while in some studies no relationship was reported. However, in a meta-analysis conducted in 2020, it was determined that individuals with rosacea had an increased risk of metabolic syndrome.¹⁸ Since metabolic syndrome is an important entity in terms of cardiovascular risk, it is valuable to examine this situation in rosacea, which is an inflammatory dermatosis. In our study, metabolic

syndrome frequency was found to be higher in individuals with rosacea compared with the control group (using the metabolic syndrome criteria of the International Diabetes Federation [IDF]). This results indicates the importance of evaluating metabolic syndrome in the first examination and follow-ups, and how valuable it is to take action on the contrary. In addition, it is obvious with these findings that rosacea requires a multidisciplinary evaluation and approach.

NLR is one of the markers showing an inflammatory state in the body, and the negative role of its elevation in cardiovascular diseases is now well-known.¹⁹ However, in research conducted by Altunışık et al., inflammatory markers such as monocyte/lymphocyte ratio, MPV, NLR, and PLR were not found statistically significant in patients with rosacea compared with healthy controls.²⁰ In our study, while the NLR was found to be significantly higher in the rosacea group, the PLR and MPV did not differ statistically between the two groups. In another statistical evaluation, when rosacea was examined in two groups as mild or moderate–severe, NLR was found to be significantly higher in moderate–severe rosacea. These results show that as the severity of inflammation increases in rosacea, NLR also increases, thus defining rosacea as an inflammatory disease. However, this finding needs to be supported by prospective studies with large series.

TABLE 6 Relationship between clinical and laboratory data of rosacea types

	Erythematotelangiectatic			Papulopustular			p		
	Mean. ± SD/n-%		Median	Mean. ± SD/n-%		Median			
Brachial diameter (initial) (cm)	3.3	±	0.3	3.2	3.4	±	0.3	3.3	0.322
Brachial diameter (after) (cm)	3.7	±	0.4	3.6	3.7	±	0.3	3.6	0.846
FMD (%)	11.7	±	6.0	9.0	8.9	±	3.4	8.0	0.038
Systolic BP (mmHg)	123.1	±	6.4	125.0	125.3	±	6.1	125.0	0.181
Diastolic BP (mmHg)	76.6	±	7.0	75.0	80.4	±	6.0	80.0	0.017
NLR	2.3	±	1.0	1.9	2.1	±	0.6	2.1	0.707
PLR	122.8	±	41.4	113.8	134.4	±	40.1	134.3	0.104
MPV (fL)	9.8	±	0.9	10.0	10.5	±	1.1	10.4	0.028
Glucose (mg/dl)	96.9	±	9.2	96.0	100.6	±	9.3	100.0	0.081
CRP (mg/L)	1.2	±	0.9	0.9	2.6	±	3.0	1.4	0.010
ESR (mm/hour)	11.3	±	12.6	6.0	7.2	±	5.6	5.0	0.692
Total Cholesterol (mg/dl)	193.5	±	27.2	195.0	188.3	±	37.1	187.0	0.210
LDL (mg/dl)	116.1	±	25.5	119.0	114.0	±	31.1	106.0	0.451
HDL (mg/dl)	51.9	±	14.4	48.0	49.5	±	12.6	49.0	0.625
Triglyceride (mg/dl)	133.3	±	85.9	103.0	124.4	±	86.0	97.0	0.451

Note: Mann–Whitney U test.

Abbreviations: BP, blood pressure; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FMD, flow-mediated dilation; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MPV, mean platelet volume; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; SD, standard deviation.

FMD was lower in PP type rosacea patients compared to ET type ($p < 0.05$). These results show that endothelial dysfunction is more prominent in PP type of rosacea.

The relationship between cardiovascular events and serum lipid levels, and CRP is well established.^{21–23} In a case–control study comparing cardiovascular risk factors in rosacea and healthy controls, individuals with rosacea were found to have higher LDL and total cholesterol levels than the control group. In addition, CRP levels of rosacea patients were significantly higher than those of the control group. HDL, triglyceride and fasting blood glucose values did not differ between the two groups.⁴ However, in our study, total cholesterol, LDL, HDL, triglyceride, and fasting blood sugar values between the two groups were statistically insignificant. Besides, the CRP levels of patients with rosacea were also not significantly higher than those of the control group. All of the above-mentioned parameters were not statistically significant when the participants were compared in two separate groups as with cutoff FMD <10% and >10%. This can be interpreted as the absence of a significant parameter for FMD in patients with rosacea severity staging. Cathelicidin, which is blamed in the etiopathogenesis of rosacea, may increase in moderate–severe rosacea patients having elevated CRP, and this vasodilator-acting molecule eliminates the known cardiac instability may lead to such a situation. However, further prospective studies are needed to uphold this idea.

Certain hematological and biochemical parameters measured in peripheral blood have been shown to correlate with disease severity in several inflammatory and cardiovascular diseases.^{24–28} Belli et al. found that NLR, CRP, systolic and diastolic BPs, total cholesterol and LDL levels were found higher in rosacea patients than in

healthy controls.²⁹ In our study, while the NLR and both systolic and diastolic BPs were significantly higher in the rosacea group, other parameters were not statistically significant. However, when the patients in the rosacea group were examined under two groups as mild and moderate–severe, no statistically significant difference was found between the two groups in systolic and diastolic BPs. On the contrary, when patients with rosacea were divided into two groups as ET and PP rosacea, diastolic BPs in PP rosacea were found to be significantly higher compared with the ET group—yet no difference was detected between systolic BPs. This supports the idea that inflammation may be more severe in PP rosacea. However, the relations of rosacea subtypes and severity need to be investigated with large series of prospective studies to support this idea.

Carotid intima-media thickness (CIMT) and epicardial fat thickness (EFT) are both ultrasonographic measurement methods used to demonstrate visceral adiposity and therefore atherosclerosis, and it has been reported that they may be independent risk factors for coronary artery disease.^{30–32} CIMT has also been accepted as a measure of occult systemic inflammation. Therefore, both methods have been examined in inflammatory dermatological diseases such as rosacea for the investigation of cardiovascular relation. Sinikumpu et al. supported the view that rosacea is a chronic systemic inflammatory disease accompanied by vascular involvement. CIMT in female rosacea patients was significantly higher compared with healthy controls.³³ In a cross-sectional study, it was determined that the EFT and CIMT of the participants with rosacea were significantly higher

TABLE 7 The relationship of disease duration with FMD, BP and laboratory values

	FMD (%)	NLR	PLR	MPV	Glu	CRP	ESR	Total cholest	LDL	HDL	Triglyce	Sys BP	Dias BP
Rosacea disease duration	R	0.167	-0.071	-0.103	0.169	0.071	0.156	0.124	0.083	-0.053	0.059	-0.006	0.006
	P	0.157	0.553	0.385	0.153	0.551	0.187	0.298	0.487	0.655	0.619	0.958	0.960

Note: r = Spearman's Correlation Coefficient.

Abbreviations: BP, blood pressure; CRP, C-reactive protein; Dias, diastolic; ESR, erythrocyte sedimentation rate; FMD, flow-mediated dilation; Glu, blood glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MPV, mean platelet volume; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; Sys, systolic.

There was no relationship between disease duration and FMD, NLR, PLR, MPV, CRP, ESR, blood glucose, total cholesterol, LDL, HDL, triglyceride, systolic & diastolic BPs ($p < 0.05$).

than the healthy controls. In addition, both systolic and diastolic BPs of rosacea patients were observed to be higher than healthy controls.²⁷ However, in another study by Ertekin et. al., comparing inflammatory blood parameters and CIMT of patients with rosacea with those of healthy controls, no difference was found between the mean CIMT of patients with rosacea and those of control groups.²⁵ Our investigation found FMD values (another method in the evaluation of early atherosclerosis) to be significantly higher in the rosacea group compared with the control group. A single method may not be adequate to conclude that rosacea is an atherosclerotic disease, and long term, prospective studies in which FMD, CIMT, EFT and electrocardiographic measurements are performed simultaneously may increase diagnostic accuracy and support the outcomes of our study.

Studies on FMD have been performed in inflammatory diseases of the skin such as psoriasis but, as far as we know, there is no study examining FMD in rosacea. In the study by Karadağ et al. on psoriasis patients and healthy controls, FMD was found to be significantly lower in psoriasis patients compared with healthy controls. It has also been reported that FMD values are lower in individuals with accompanying psoriatic arthritis.⁷ This study supports the view that inflammation in psoriasis causes a decrease in FMD. On the contrary, in another study, FMD value was not found to be lower than in healthy controls.³⁴ These contradictory findings show that prospective studies with large series are needed to define and evaluate cardiovascular disease risks in inflammatory skin diseases.

In our study, when patients with rosacea were analyzed under two groups as mild and moderate-severe, it was found that forehead involvement was significantly higher in the moderate-severe group than in the group with mild involvement. This leads to the assumption that forehead involvement may be more frequent in severe involvement. However, we could not find any information on record to confirm that forehead involvement creates a stronger inflammatory response. Prospective, long-term studies are needed to support this view.

In research conducted by Belli et al., it was reported that individuals with PP type rosacea have a higher cardiovascular risk than patients with ET type rosacea.²⁷ In our study, diastolic arterial BP, MPV, and CRP levels were found to be significantly higher in PP patients compared with ET type patients. This finding is consistent with the literature mentioned above. However, the higher number of ET type patients in the mild group may have affected this result in our study. It should also be noted that ET type rosacea was more common in the above-mentioned study.²⁷ In the linear regression analysis, a significant relationship was found between rosacea type and FMD. Thus, inflammation may be more severe in PP type rosacea. However, this needs to be researched with larger series. Systemic suppression of TNF alpha at the end of the cascade by molecular cathelicidin of the ET type may explain the interruption in the vascular and cardiac extent of inflammation. Conducting and evaluating more molecular studies on this subject will shed light on the issue.

Our study has some limitations as an observational case-controlled study conducted in a single center. Only ultrasonographic

TABLE 8 Results of multivariate linear regression analysis in which FMD score is the dependent variable

	Unstandardized coefficients		Standardized coefficients		95.0% confidence interval for B	
	B	Std. Error	Beta	p	Lower Bound	Upper Bound
Rosacea type	0.187	0.088	0.250	0.038	0.011	0.364

Rosacea type significantly predicted the AAD score in linear regression analysis ($p < 0.05$).

FMD measurement was used to evaluate the risk of subclinical atherosclerosis. Other methods such as EFT, CIMT, echocardiographic and electrocardiographic measurements were not performed. Nutrition, which is one of the factors that may personally affect the development of subclinical atherosclerosis, was not considered in this study. Research in which these parameters are evaluated jointly will be beneficial.

5 | CONCLUSION

The main purpose of this study is to evaluate possible endothelial dysfunction, and thus early atherosclerosis in rosacea by flow-mediated dilatation method. In addition, the evaluation process of this relationship was strengthened by using various inflammatory and proatherogenic hematological and biochemical markers. NLR, which is one of the inflammatory markers, was found to be high in the rosacea group. Besides, FMD was low compared with the control group, indicating endothelial dysfunction. In the light of these data, it is not inaccurate to conclude that rosacea is not a disease limited to the skin, but may affect the cardiovascular system. Patients with a diagnosis of rosacea should be evaluated for early prevention of possible cardiovascular complications. This study is unique evaluating endothelial dysfunction in rosacea, and it enlightens the clinicians about the importance of the assessment of cardiovascular risks during the examination process of these patients.

AUTHOR CONTRIBUTIONS

Conception and design of the study: Nazlı Caf, Tuğba Özkök Akbulut, Mehmet Mustafa Can, Zafer Türkoğlu; acquisition of data: Nazlı Caf, Mustafa Sarı; analysis and/or interpretation of data: Nazlı Caf, Mustafa Sarı, Zafer Türkoğlu, Mehmet Mustafa Can, Nilhan Atsü; drafting article: Nazlı Caf, Tuğba Özkök Akbulut, Mustafa Sarı; Revision of the manuscript: Zafer Türkoğlu, Mehmet Mustafa Can, Tuğba Özkök Akbulut, Nazlı Caf.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

We conducted our study according to the World Medical Association Declaration of Helsinki and acquired the approval of the local ethics committee (Health Sciences University Başakşehir Çam and Sakura City Hospital, İstanbul with decision number: 2021-12).

INFORMED CONSENT

Written and informed consent was obtained from all the participants of the study.

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