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Posted Date: 17 December 2024

doi: 10.20944/preprints202412.1401.v1

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Relationship of Biochemical and Sonographic Markers with Disease Severity in Rosacea Patients Without Cardiovascular Disease

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Abstract: Rosacea is a chronic skin condition characterized by inflammatory lesions. Inflammation plays an important role in all stages of atherosclerosis, yet there is debate in the literature regarding whether rosacea is a systemic inflammatory disease and its association with cardiovascular diseases. This study aims to investigate this potential relationship by assessing biochemical markers and sonographic findings in rosacea patients and disease severity groups. Our study included 73 rosacea patients and 73 age- and sex-matched controls, without cardiovascular risk factors. Demographic, clinical, and laboratory data were recorded for all participants. Carotid intima-media thickness and the thickness of subcutaneous, preperitoneal, posterior perirenal, and aortic-level visceral adipose tissues were measured by ultrasonography. The erythrocyte sedimentation rate was significantly elevated in rosacea patients versus controls. Additionally, sonographic assessments revealed that both aortic-level visceral adipose tissue and preperitoneal adipose tissue were significantly thicker in rosacea patients than in the control group, a finding corroborated by multivariate linear regression analysis. While thicker preperitoneal and perirenal adipose tissues were observed with increasing disease severity, these differences did not achieve statistical significance when subjected to multivariate linear regression analysis. Our findings support the association between rosacea and cardiovascular risk. The thorough examination and follow-up of patients with rosacea for cardiovascular risk factors may be necessary in clinical practice.

Keywords: rosacea; atherosclerosis; cardiovascular

1. Introduction

Rosacea is a chronic inflammatory skin condition characterized by episodic flushing followed by persistent central erythema, telangiectasias, red papules, and pustules, and in some cases, phymatous or granulomatous changes. Ocular symptoms can also be associated with the condition. Rosacea predominantly affects fair-skinned women over the age of thirty [1]. Although numerous studies have been conducted on the etiopathogenesis of rosacea, genetic predisposition, neurovascular dysregulation, activation of the innate immune system, and environmental factors are believed to play significant roles.

There are perspectives suggesting that rosacea is a systemic inflammatory condition rather than merely a skin disorder, and it may be associated with various systemic diseases. Numerous studies have been conducted to assess the comorbidities associated with rosacea. Research indicates that

 doi:10.20944/preprints202412.1401.v1

rosacea is linked to various conditions, including thyroid disorders, cardiovascular diseases, gastrointestinal disorders, neurological conditions, and malignancies [2].

The relationship between rosacea and cardiovascular diseases remains controversial [3,4]. However, it has been identified that rosacea and atherosclerosis share common pathogenic features, including increased oxidative stress, elevated levels of cathelicidin in inflammatory cells, and reduced levels of anti-inflammatory agents [2]. Moreover, chronic systemic inflammation is thought to initiate and accelerate the atherosclerotic process by causing endothelial dysfunction [5].

Increased visceral adipose tissue (VAT) contributes to the progression of atherosclerosis independently of obesity by promoting the release of proinflammatory cytokines [6,7]. Carotid intima-media thickness (CIMT) is associated with subclinical atherosclerosis and serves as an important marker in assessing cardiovascular risk [8].

In this study, we aimed to evaluate the relationship between rosacea and biochemical parameters, VAT, and CIMT values.

2. Materials and Methods

2.1. Study Population

We conducted a cross-sectional study involving rosacea patients aged 18 years and older, as well as age- and gender-matched controls, at the Department of Dermatology, Nigde Omer Halisdemir University Training and Research Hospital, between February 2024 and August 2024. Prior to the study, we obtained approval from the ethics committee. Participants in both the rosacea and control groups were selected consecutively based on specific inclusion and exclusion criteria.

Patients and controls meeting any of the following criteria were excluded from the study: a history of cardiac and/or cerebrovascular disease, diabetes mellitus (defined as a fasting blood sugar level ≥126 mg/dL), hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg), dyslipidemia (total cholesterol level ≥200 mg/dL, triglyceride level ≥150 mg/dL, or high-density lipoprotein [HDL] cholesterol level ≤40 mg/dL), chronic kidney disease (glomerular filtration rate <60), a diagnosis of connective tissue and/or inflammatory bowel disease, obesity (body mass index >30), a history of smoking, the use of medications affecting the cardiovascular system (such as antihypertensive, antihyperlipidemic, antidiabetic, or anticoagulant drugs), and those with only ocular involvement.

Rosacea patients were divided into 3 subtypes: erythematotelangiectatic rosacea (ETR), papulopustular rosacea (PPR), and phymatous rosacea (PR). Disease severity was assessed according to the rosacea clinical severity index proposed by the National Rosacea Society Expert Committee [9]. Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Sedimentation rate (ESR), C-reactive protein (CRP), and complete blood count values of patients and controls were recorded.

2.2. Imaging Procedures

Sonographic measures were acquired by a radiologist utilizing an ultrasound device (Samsung Medison V8; Samsung Healthcare, Korea). A 3.5 MHz curved-array probe was employed to assess adipose tissue parameters 'a', 'b', 'c', and 'd', as detailed below: a: thickness of subcutaneous adipose tissue at the xiphoid process; b: thickness of pre-peritoneal adipose tissue at the xiphoid process; c: distance between the posterior wall of the aorta and the internal surface of the rectus abdominis muscle at the level of the umbilicus (VAT-aorta); d: thickness of right posterior perirenal adipose tissue (VAT-perirenal) [10]. Parameters 'c' and 'd' pertain to VAT.

Furthermore, carotid intima-media thickness (CIMT) was assessed utilizing an 11 MHz linear array probe on the same device. CIMT values were assessed at the conclusion of diastole and analyzed in the longitudinal view, focusing on non-plaque segments of each common carotid artery. All measurements were acquired after an overnight fast, essential for abdominal parameter assessment, and all data were collected in the supine position at the end of expiration. To avoid compressing adipose tissue, a curvilinear transducer was placed perpendicular to the skin with minimal pressure.

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2.3. Statistical Analyses

Statistical analyses were conducted using Jamovi Statistics Software (Version 2.3.28.0). Descriptive statistics for the study population are reported as proportions, means, or medians, depending on the data distribution. The normality of numeric variables was assessed using the Shapiro-Wilk test and Q-Q plots. Comparisons of quantitative variables were performed using either the Student's t-test or the Mann-Whitney U test, based on the distribution of the data. Qualitative variables were analyzed using the Pearson chi-square test or Fisher's exact test, as appropriate. Multivariate linear regression models were employed to assess the association of numerical or categorical independent variables with continuous dependent variables. A significance threshold of 0.05 was applied for all statistical tests.

3. Results

A total of 73 rosacea patients and 73 age- and sex-matched controls were included in the study. Demographic, clinical, and laboratory data for the patients and controls are presented in Table 1. There was no significant difference in BMI between the control and patient groups but the patient group had significantly lighter skin types according to the Fitzpatrick scale. Fifty-one (69.9%) of the patients had ETR, 20 (27.4%) had PPR and 2 (2.7%) had PR. According to the disease severity index (9), 19 (26.0%) of the patients had mild disease, 48 (65.8%) had moderate disease, and 6 (8.2%) had severe disease. Seventeen (23.3%) of the patients had also ocular involvement.

The mean ESR value in rosacea patients was significantly higher than in the control group (15.10±10.8 vs 6.86±3.05; p<0.01). No significant difference was found in terms of CRP, lymphocyte, neutrophil, and platelet counts, mean platelet volume, neutrophil/lymphocyte ratio (NLR), and platelet/lymphocyte ratio.

According to sonographic findings, preperitoneal adipose tissue at the xiphoid process level (14.11±4.47 vs 11.0±3.12; p<0.001) and VAT-aorta (36.9±16.26 vs 25.57±6.32; p<0.001) were found to be significantly thicker in rosacea patients compared to the control group. However, no significant differences existed in CIMT, subcutaneous adipose tissue, and VAT-perirenal thickness.

Table 1. Distribution of the obtained parameters and demographic data between the rosacea and control groups.

Variables	Rosacea, n=73	Control , n=73	P value
Age, year, mean ± SD	37.7±11.3	37.7±11.3	0.994
Men/Women, n	9/64	9/64	1
Fitzpatrick skin type, n (%)			**0.036**
I	3 (4.1%)	0 (0%)	
II	21 (28.8%)	12 (16.4%)	
III	35 (47.9%)	36 (49.3%)	
IV	14 (19.2%)	25 (34.2%)	
Subtype of rosacea, n (%)			
ET	51 (69.9%)		
PP	20 (27.4%)		
Phymatous	2 (2.7%)		
Disease Severity			
Mild	19 (26.0%)		
Moderate	48 (65.8%)		
Severe	6 (8.2%)		

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Eye Involvement, n (%) Yes No	 17 (23.3%) 56 (76.7%)		
BMI, kg/m2, mean ± SD	25.0±2.67	25.2±2.80	0.62
ESR mm/first h, mean ± SD	15.10±10.8	6.86±3.05	**<0.01**
CRP	3.03±3.16	2.97±2.64	0.77
Neutrophil Count, K/mL, mean ± SD	4.30±1.44	4.29±1.38	0.91
Lymphocyte Count	2.51±0.61	2.61±0.64	0.35
Platelet Count	323.986±60.390	325.575±58.896	0.87
NLR	1.74±0.56	1.68±0.52	0.533
PLR	134.19±36.44	130.27±35.79	0.514
MPV	10.35±0.88	10.38±0.74	0.69
Subcutaneous fat-xiphoid	14.09±5.09	14.09±5.01	0.99
Preperitoneal fat-xiphoid	14.11±4.47	11.0±3.12	**<0.001**
VAT-aorta	36.9±16.26	25.57±6.32	**<0.001**
VAT-perirenal	8.23±1.86	8.13±1.77	0.84
Mean Carotid IMT	0.77±0.19	0.77±0.21	0.94

ET: Erythematotelangiectatic Subtype, PP: Papulopustular Subtype, BMI: Body Mass Index, ESR: Erythrocyte Sedimentation Rate, CRP: C-reactive Protein, NLR: Neutrophil-to-Lymphocyte Ratio, PLR: Platelet-to-Lymphocyte Ratio, MPV: Mean Platelet Volume, IMT: Intima-Media Thickness.

We evaluated demographic, laboratory, and sonographic findings based on disease severity, subtype, and ocular involvement (Table 2). Patients were categorized into mild and moderate-severe groups according to disease severity. In the moderate-severe group, age (39.4±11.5 vs 32.8±9.4; p=0.02) and BMI (25.3±2.5 vs 23.8±2.8; p=0.03) were significantly higher, and preperitoneal adipose tissue (14.9±4.2 vs 11.6±4.2; p=0.008) and VAT-perirenal (8.5±1.9 vs 7.4±1.4 p=0.049) were notably thicker compared to the mild disease. The findings did not reveal significant differences concerning ocular involvement and disease subtype.

Table 2. Distribution of obtained parameters and demographic data according to disease severity, eye involvement and disease subtype.

	Disease Severity			Eye Involvement			Rosacea Subtype		
Variables	Mild (19)	Moderate-Severe(54)	P value	Yes (17)	No (56)	P value	ET (51)	PP(20)	P value
Age, year, mean ± SD	32.8±9.4	39.4±11.5	**0.02**	39.9±10.6	37.0±11.5	0.35	37.4±11.6	36.8±10.0	0.88
Sex Men Women	 2(10.5%) 17(89.5%)	 7(13%) 47(87%)	0.78	 1(5.1%) 16 (94.1%)	 8(14.3%) 48(85.7%)	0.35	 6(11.8%) 45(88.2%)	 3(15%) 17(85%)	0.71

 doi:10.20944/preprints202412.1401.v1

BMI, kg/m2, mean ± SD	23.8±2.8	25.3±2.5	**0.03**	25.4±2.1	24.8±2.8	0.37	24.5±2.6	25.7±2.3	0.07
ESR mm/first h, mean ± SD	17.0±16.5	14.4±8.0	0.99	15.7±6.2	14.9±11.9	0.17	15.7±11.7	13.1±8.5	0.35
CRP	3.3±2.9	2.92±3.2	0.84	2.9±2.1	3.0±3.4	0.50	3.2±3.3	2.4±2.7	0.15
Neutrophil count, K/mL, mean ± SD	4.0±0.9	4.4±1.5	0.57	4.4±1.6	4.2±1.3	0.91	4.2±1.4	4.6±1.4	0.21
Lymphocyte count	2.4±0.4	2.5±0.6	0.54	2.4±0.5	2.5±0.6	0.51	2.4±0.5	2.6±0.7	0.48
Platelet Count	305.8±61.0	330.3±59.4	0.12	344.5±44.4	317.7±63.4	0.10	318.9±59.9	338.5±61.9	0.22
NLR	1.66±0.47	1.77±0.60	0.62	1.68±0.35	1.76±0.41	0.58	1.72±0.54	1.78±0.47	0.49
PLR	127±25.76	136.7±39.4	0.37	124.8±33.2	138.3±36.5	0.33	131.4±29.2	137.2±38.1	0.41
MPV	10.6±1.20	10.28±0.72	0.33	10.2±0.91	10.55±0.7	0.44	10.6±1.1	10.15±0.85	0.52
Subcutaneous fat-xiphoid	12.9±5.5	14.5±4.8	0.31	15.1±6.2	13.7±4.7	0.34	13.6±4.9	14.5±5.1	0.50
Preperitoneal fat-xiphoid	11.6±4.2	14.9±4.2	**0.008**	14.6±5.3	13.9±4.2	0.57	13.5±4.2	14.8±4.7	0.28
VAT-aorta	31.7±10.4	38.7±17.6	0.22	37.4±16.7	36.7±16.2	0.88	34.6±16.1	39.9±14.8	0.12
VAT-perirenal	7.4±1.4	8.5±1.9	**0.049**	8.8±2.1	8.0±1.7	0.24	8.0±1.7	8.3±1.8	0.35
Carotid Mean	0.7±0.1	0.7±0.2	0.11	0.8±0.2	0.7±0.1	0.11	0.7±0.1	0.7±0.1	0.45

ET: Erythematotelangiectatic Subtype, PP: Papulopustular Subtype, BMI: Body Mass Index, CRP: C-reactive Protein, NLR: Neutrophil-to-Lymphocyte Ratio, PLR: Platelet-to-Lymphocyte Ratio, MPV: Mean Platelet Volume.

When the significant sonographic findings were re-evaluated using multivariate linear regression analysis, VAT-aorta and preperitoneal fat tissue at the xiphoid level remained significant ($p<0.001$). However, the association between rosacea severity and both preperitoneal adipose tissue and VAT-perirenal was not significant. The results of multivariate linear regression analysis are shown in Table 3.

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Table 3. Multivariate linear regression analyses of significant parameters.

Independent predictors for *preperitoneal fat* by multivariate linear regression analysis; Rosacea vs Control					
Variables	Estimate	Standart Error	%95 CI	t	P Value
Age	0,06	0,03	0,01 - 0,11	1,99	0,04
Gender	0,03	0,8	-1,56 - 1,62	0,03	0,97
BMI	0,67	0,11	0,44 - 0,89	5,85	0,01
Presence of Rosacea	3,22	0,52	2,18 - 4,27	6,12	0,01
Independent predictors for *VAT-aorta* by multivariate linear regression analysis; Rosacea vs Control					
Variables	Estimate	Standart Error	%95 CI	t	P Value
Age	0,21	0,09	0,04 - 0,39	2,45	0,01
Gender	5,21	2,58	0,11 - 10,33	2,02	0,04
BMI	1,97	0,37	1,24 - 2,70	5,36	0,01
Presence of Rosacea	11,67	1,69	8,33 - 15,02	6,91	0,01
Independent predictors for *preperitoneal fat* by multivariate linear regression analysis, in group of rosacea patients					
Variables	Estimate	Standart Error	%95 CI	t	P Value
Age	0,04	0,04	-0,04 - 0,13	0,95	0,34
Gender	0,85	1,29	-1,73 - 3,43	0,65	0,51
BMI	0,79	0,19	0,42 - 1,17	4,22	0,01
Rosacea Severity	1,84	1	-0,16 - 3,85	1,83	0,07
Independent predictors for *VAT-perirenal* by multivariate linear regression analysis, in group of rosacea patients					
Variables	Estimate	Standart Error	%95 CI	t	P Value
Age	0,05	0,02	0,01 - 0,08	2,96	0,01
Gender	0,28	0,49	-0,69 - 1,25	0,58	0,56
BMI	0,33	0,07	0,19 - 0,47	4,66	0,01
Rosacea Severity	0,26	0,38	-0,49 - 1,01	0,69	0,49

4. Discussion

There is increasing evidence that rosacea is a systemic inflammatory disease rather than a skin disease [11]. The antimicrobial peptide cathelicidin has been shown to be elevated in patients with rosacea. Beyond its antimicrobial properties, cathelicidin has proinflammatory functions that enhance the release of cytokines and chemokines, thereby stimulating the innate immune system through multiple pathways. Furthermore, cathelicidin promotes endothelial cell proliferation and angiogenesis [12]. Clinical studies with rosacea patients have found that inflammatory markers are higher in this group compared to controls, supporting the view that rosacea is a systemic inflammatory disease. Karaosmanoglu et al. analyzed commonly used inflammatory markers in the blood of rosacea patients and observed that ESR, CRP, MPV, and SII index values were significantly elevated relative to the control group [13]. Similarly, another study by Ertekin et al. assessed serum proinflammatory cytokine levels, finding that hs-CRP, TNF-α, IL-1β, and IL-6 were higher than those

 doi:10.20944/preprints202412.1401.v1

in the control group [14]. In our study, supporting the literature, ESR values were found to be significantly higher in rosacea patients than in the control group.

Inflammation is an important factor at every stage of atherosclerosis and its complications. During the early phases of atherosclerosis, monocytes that have ingested oxidized lipids migrate to the affected area and differentiate into macrophages and foam cells, thereby forming fatty streaks. Subsequently, the influx of additional inflammatory mediators facilitates the formation of an atheroma plaque. This plaque becomes prone to rupture as collagen is degraded by metalloproteinases secreted by monocytes and macrophages. Recent research has identified that similar biological pathways are involved in both rosacea and atherosclerosis [15]. Notably, cathelicidin is increases, and the activity of the antioxidant enzyme serum paraoxonase-1 (PON), which metabolizes lipid peroxides and prevents oxidative modification of serum lipoproteins, decreases during both conditions [2]. Given these findings, cardiovascular risk factors have been explored in rosacea patients. A 2014 case-control study revealed that individuals with rosacea had higher incidences of dyslipidemia, smoking, alcohol consumption, and a family history of cardiovascular disease compared to control subjects [16]. Similarly, a case-control study conducted in Taiwan identified associations between rosacea and conditions such as dyslipidemia, coronary artery disease, and hypertension. The link between coronary artery disease and rosacea remained significant even after adjusting for diabetes, hypertension, and dyslipidemia [16]. In contrast, a study by Egeberg et al. reported no significant association between rosacea and cardiovascular risk factors or mortality [4]. Furthermore, a 2020 meta-analysis indicated that rosacea is associated with hypertension and dyslipidemia, but not with ischemic heart disease, stroke, or diabetes [17].

The conflicting findings regarding the relationship between rosacea and cardiovascular disease have led researchers to investigate the objective measures of atherosclerosis, which underlies cardiovascular conditions [18]. Akın Belli et al. examined epicardial fat tissue and CIMT as indicators of subclinical atherosclerosis in rosacea patients and discovered that both measures were significantly elevated compared to the control group [19]. Conversely, in another study, Ertekin et al. assessed the CIMT in both rosacea patients and control groups but found no significant differences between them [14]. Additionally, Caf et al. measured flow-mediated dilation in rosacea patients to assess endothelial dysfunction, an early indicator of atherosclerosis. They observed that flow-mediated dilation, which negatively correlates with endothelial dysfunction, was significantly reduced in rosacea patients [20].

Adipose tissue functions as a secretory organ, producing adipokines and proinflammatory cytokines [21]. Although obesity is recognized as a cardiovascular risk factor, the importance of adipose tissue distribution and the association between increased visceral adipose tissue and atherosclerosis have also been emphasized in non-obese patients. Research has indicated that VAT is linked to atherosclerosis in non-obese individuals [22,23]. Additionally, preperitoneal adipose tissue has been identified as associated with atherosclerosis and is considered a critical parameter for the early prediction of this condition [23]. In our study, we examined subcutaneous adipose tissue, preperitoneal adipose tissue, CIMT, and VAT values from two areas in rosacea patients without cardiovascular risk factors. Both VAT and preperitoneal adipose tissue thickness were significantly higher in rosacea patients compared to the control group. These findings retained their significance upon confirmation through multivariate linear regression analysis. When we analyzed our parameters based on the severity of rosacea, we observed an increase in VAT and preperitoneal fat tissue thickness with increasing severity of rosacea, although this trend did not reach statistical significance in the multivariate regression analysis. Consistent with the existing literature, our findings support the association between rosacea and atherosclerosis. Nonetheless, we did not observe a significant impact of rosacea severity or subtype on this association.

The limitations of our study include a relatively small sample size and its design as a single-center investigation.

5. Conclusions

In our study, we observed that ESR was elevated in comparison to the control group, reinforcing the concept that rosacea is a systemic inflammatory disease. Additionally, the thicknesses of visceral

 doi:10.20944/preprints202412.1401.v1

and preperitoneal fat tissues, which are critical in predicting atherosclerosis, were found to be increased in rosacea patients relative to controls. While these results support the link between rosacea and cardiovascular diseases, further research with a larger cohort is warranted to substantiate this relationship. Given these findings, we recommend close monitoring for cardiovascular risk factors in this patient group.

Author Contributions: All authors have read and approved the final manuscript. BİM: Conceptualization, Data Mining, Writing and Editing; BARM: Conceptualization, Data Mining, Writing and Editing; BF: Supervision MFA: Statistics and Writing

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Nigde Omer Halisdemir University Faculty of Medicine (Protocol code: 2024/116).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data featured in this work can be obtained with a special request from the corresponding author.

Conflicts of Interest: The authors declare no conflicts of interest.

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