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# Carotid intima-media thickness and serum proinflammatory cytokine levels in rosacea patients without cardiovascular risk factors

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## Abstract

There is a growing body of evidence linking rosacea to various systemic disorders, even though data regarding the association between rosacea and cardiovascular diseases are presently controversial. We sought to investigate the potential association of rosacea with subclinical atherosclerosis and serum proinflammatory/proatherogenic markers. This study included 44 patients with rosacea and 44 age-matched and sex-matched healthy control subjects. Patients with traditional cardiovascular risk factors or a history of cardiovascular events were excluded. Demographic, clinical, and laboratory data, including serum interleukin-1 beta (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and high-sensitivity C-reactive protein (hs-CRP) levels were assessed. Carotid intima-media thickness (CIMT) and carotid plaques were measured by carotid ultrasonography. Serum IL-1β ($P < .001$), IL-6 ($P < .001$), TNF-α ($P < .001$), and hs-CRP ($P < .001$) levels were significantly higher in the patient group compared with the control group. Mean CIMT values did not differ significantly between the patient group and control group ($P > .05$). Patients with moderate to severe rosacea had a significantly greater CIMT than those with mild rosacea ($P = .047$). Rosacea patients with eye involvement had a significantly greater CIMT than those without eye involvement ($P = .008$). There was no significant correlation between CIMT values and inflammation parameters. As conclusion, in the absence of other traditional cardiovascular risk factors, rosacea does not seem to affect mean CIMT value. However, specific subgroups such as patients with moderate to severe disease or with eye involvement are associated with increased subclinical atherosclerosis and may require additional attention for cardiovascular disease prevention.

**KEYWORDS**
atherosclerosis, cardiovascular diseases, carotid intima-media thickness, cytokines, rosacea

## 1 | INTRODUCTION

Rosacea is a chronic, inflammatory skin disease characterized by prominent facial erythema, papules, pustules, and occasionally permanent phymatous changes. The etiopathogenesis is not completely understood, although immune dysregulation, neurovascular dysregulation, and genetic factors seem to play a significant role.[1-4]

  

Several recent epidemiological studies have reported potential associations of rosacea with various systemic comorbidities; raising the question of whether it is a disease with systemic implications rather than a localized skin disease.[5-7] In this regard, reports have shown higher serum oxidative stress levels in patients with rosacea than control subjects, supporting the hypothesis that the chronic inflammation of rosacea may not only be limited to the skin.[8,9]

Data regarding the association between rosacea and cardiovascular diseases (CVD) are presently controversial.[10-15] Chronic inflammatory diseases, such as psoriasis vulgaris and rheumatoid arthritis, have been shown to have a higher cardiovascular morbidity and mortality burden than the general population and have been associated with an increased prevalence of subclinical atherosclerosis.[16-18] Chronic systemic inflammation is thought to induce and accelerate the atherosclerotic process by causing endothelial disfunction.[19] The measurement of carotid intima-media thickness (CIMT) using carotid ultrasonography is an accepted surrogate marker for subclinical atherosclerosis, which enables the risk assessment of CVD in an individual.[20-22]

In this study, we sought to investigate the potential association of rosacea with subclinical atherosclerosis and some serum proinflammatory/proatherogenic markers, including serum interleukin-1 beta (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and high-sensitivity C-reactive protein (hs-CRP).

## 2 | METHODS

### 2.1 | Study population

We performed a cross-sectional case-control study at a single dermatology unit in Istanbul. From January 2018 to April 2018, consecutive Caucasian patients over 18 years of age with a clinical diagnosis of rosacea were recruited from our dermatology outpatient clinic. A sex-matched and age-matched control population was selected from the medical and administrative personnel from our hospital. The study was approved by the local institutional ethics committee, and all included subjects gave their informed consent to the study and investigation.

Patients and control subjects with any one of the following were excluded: (a) documented history of CVD, including coronary artery disease, heart failure, stroke, or peripheral arterial disease; (b) type 1 or type 2 diabetes mellitus (fasting blood glucose level ≥126 mg/dL); (c) hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg); (d) dyslipidemia (total cholesterol level ≥200 mg/dL, triglyceride level ≥150 mg/dL, or high-density lipoprotein [HDL] cholesterol level ≤40 mg/dL); (e) chronic kidney disease (serum creatinine values ≥1.3 mg/dL); (f) smoking; (g) presence of concomitant dermatological or systemic inflammatory diseases, such as psoriasis vulgaris, rheumatoid arthritis, connective tissue disease, and inflammatory bowel disease; or (h) taking medication that affects the cardiovascular system (antihypertensive, antihyperlipidemic, antidiabetic, or anticoagulant). Rosacea patients with only eye involvement were also not included in the study.

Height, weight, and blood pressure were measured for each subject. Body mass index (BMI) was calculated using the formula: weight (kg)/height$^2$ (m$^2$).

The patients diagnosed with rosacea were classified into the following three clinical subtypes types: Type 1—erythematotelangiectatic rosacea (ETR), Type 2—papulopustular rosacea (PPR), and Type 3—phymatous rosacea (PR). Disease severity was calculated using the rosacea clinical severity index proposed by the National Rosacea Society Expert Committee.[23] Regardless of the existence of any subjective eye complaints, an ophthalmological examination was performed for every patient to determine ocular involvement.

### 2.2 | Laboratory examinations

After overnight fasting, venous blood samples were extracted from every subject and complete blood count, glucose, total cholesterol, low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), triglycerides, and erythrocyte sedimentation rate (ESR) were determined.

An additional venous sample was obtained and placed into tubes containing gel additive. The contents were centrifuged at 3500*g* for 10 minutes to separate the plasma and were then stored in aliquots at −80°C until needed. Serum IL-1β, IL-6, TNF-α, and hs-CRP levels were determined by commercial enzyme-linked immunosorbent assays (ELISA) according to the manufacturer's instructions (Elabscience Biotechnology Co. Ltd, Wuhan, China).

### 2.3 | Carotid ultrasonographic study

The study was performed using carotid duplex high-resolution B-mode ultrasonography equipment (Aplio 400, Toshiba Canon Medical Systems Europe B.V., Netherlands) with a 9.2- to 14-MHz linear-array transducer. Patients and controls were examined in supine position with the neck extended and the chin rotated in the opposite direction to the side being examined. CIMT was measured at the end-diastolic phase in the posterior wall of the common carotid artery, 1 cm below the carotid bifurcation (Figure 1). The CIMT measurement was performed automatically, using the device's software, which performs three different automatic measurements of the selected segment and obtains an average value. These measurements were performed bilaterally and the average of the left and right CIMT values comprised the "mean CIMT" value for the analysis.

The carotid artery tract was scanned for the presence of plaque from the supraclavicular level to the mandible. According to the Mannheim Carotid Intima-Media Thickness Consensus recommendations, a carotid plaque was defined as the presence of focal wall thickening at least 50% greater than that of the surrounding IMT, or as a focal thickness of ≥1.5 mm that protrudes into the lumen.[24]

All tests were carried out by a single experienced sonographer who was blinded to the clinical and laboratory status of the patients and controls.

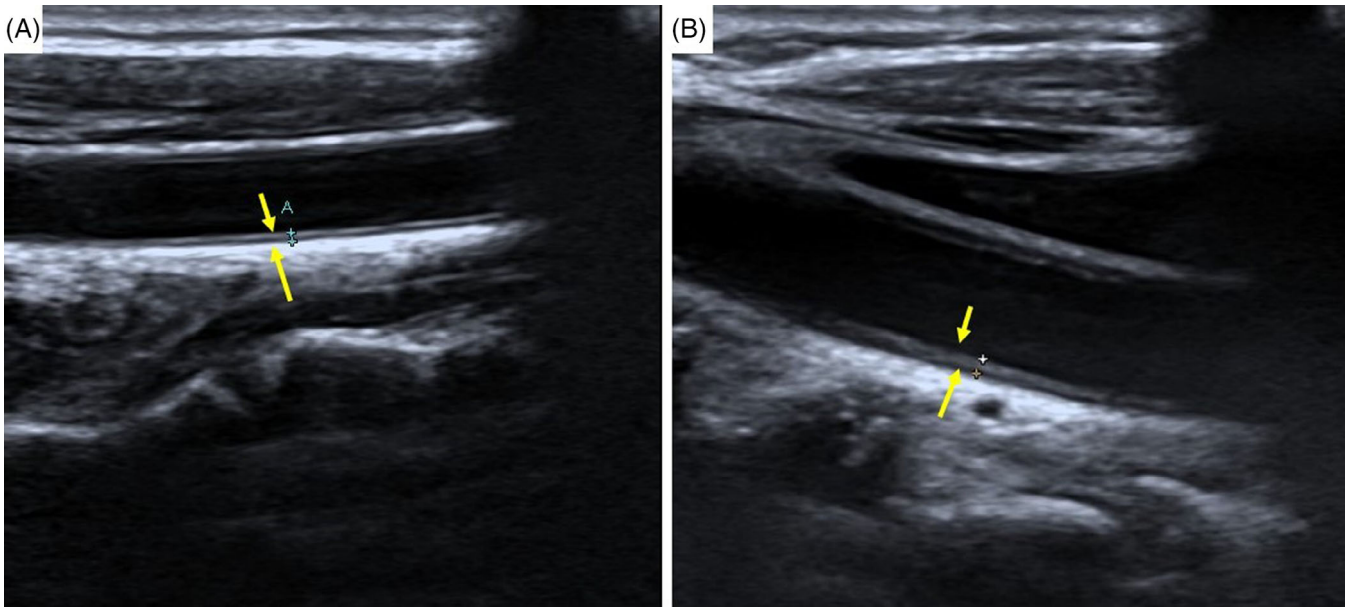


**FIGURE 1** Sonographic assessment of the carotid intima-media thickness (CIMT). A, Showing normal CIMT of one of the patients, CIMT = 0.5 mm. B, Showing increased CIMT of one of the patients, CIMT = 0.9 mm

### 2.4 | Statistical analyses

Statistical analysis was performed using IBM SPSS Statistics for Windows v.22.0. (IBM Corp., Armonk, New York). The characteristics of the study population are presented as proportions, means, or medians as appropriate. The Shapiro-Wilk test was used to determine the normality of the distribution of numeric variables. Quantitative variables were compared using the Student *t* test or Mann-Whitney *U* test as appropriate. For the comparison of quantitative variables for more than two groups, one-way analysis of variance (ANOVA) or the Kruskal-Wallis test was utilized. The Pearson $x^2$ test or Fisher exact test was used to compare the qualitative variables. Spearman's correlation analysis was performed to determine the relationship between two continuous variables. A significance level of 5% was used.

## 3 | RESULTS

### 3.1 | Demographic and clinical data

A total of 44 patients with rosacea and 44 healthy control subjects were included in the study. The main demographic and clinical data are summarized in Table 1. Sex distribution, mean age, and Fitzpatrick skin type did not significantly differ between the patients and control subjects. The mean duration of rosacea was 5.2 ± 5.0 years. About 25 patients (56.8%) had ETR, 17 patients (38.6%) had PPR, and only 2 patients (4.5%) had FR. About 11 patients (25%) were classified as having mild disease, 25 patients (56.8%) as having moderate disease, and the remaining 8 (18.2%) as having severe disease. Out of 44 rosacea patients included in the study; 16 patients (36.4%) did not receive any treatment for rosacea before or at the time study. About 12 patients (27.3%) received topical treatments alone, while 16 patients (36.4%) received oral treatment with or without topical treatment. Eye involvement was present in 28 (63.6%) of the patients.

### 3.2 | Laboratory and carotid ultrasound findings

Patients with rosacea showed significantly higher serum IL-6 ($P < .001$), IL-1β ($P < .001$), TNF-α ($P < .001$), and hs-CRP ($P < .001$) levels compared with the control subjects (Table 2). Fasting glucose, lipid profiles, ESR, neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and mean platelet volume (MPV) were not statistically different between the two groups.

The IMT values of the left and right common carotid artery and the mean IMT value of both did not differ significantly between the two groups (Table 2). The mean CIMT value for rosacea patients was 0.59 ± 0.08 mm, and 0.62 ± 0.09 mm for control subjects ($P = .098$). Carotid plaque frequency was similar between patients with rosacea (n = 2.5%) and the control subjects (n = 3.7%), and the difference was not statistically significant ($P = .65$; Table 2).

Laboratory and CIMT findings were separately evaluated for the ETR and PRP subtypes. Patients with FR were not included in this analysis, as there were only two patients. Mean CIMT, IL-6, IL-1β, TNF-α, hs-CRP, N/L ratio, P/L ratio, and MPV values did not significantly differ between the ETR and PRP subtypes (Table 3).

For further analyses in respect to disease severity, patients with moderate and severe disease were combined into a moderate-severe group and compared with patients with mild disease. Patients with moderate-severe disease had a significantly greater mean CIMT than patients with mild disease (0.61 ± 0.08 vs 0.55 ± 0.08 mm; $P = .047$). IL-6, IL-1β, TNF-α, hs-CRP, N/L ratio, P/L ratio, and MPV values were not statistically different between the two groups (Table 3).

**TABLE 1** Demographic and clinical findings of patients with rosacea and healthy control subjects

| Variable | Rosacea, n = 44 | Control, n = 44 | *P* |
|---|---|---|---|
| Age, year, mean ± SD | 40.6 ± 10.9 | 40.8 ± 11.2 | .98 |
| Men/women, n | 12/32 | 12/32 | 1.000 |
| Fitzpatrick skin type, n (%) | | | |
| II | 14 (31.8) | 14 (31.8) | .435 |
| III | 22 (50.0) | 26 (59.1) | |
| IV | 8 (18.2) | 4 (9.1) | |
| Age of onset of rosacea, mean ± SD | 35.4 ± 11.0 | – | – |
| Disease duration, mean ± SD | 5.2 ± 5.0 | – | – |
| Subtype of rosacea, n (%) | | | |
| ETR | 25 (56.8) | – | – |
| PPR | 17 (38.6) | | |
| Phymatous | 2 (4.5) | | |
| Disease severity, n (%) | | | |
| Mild | 11(25.0) | – | – |
| Moderate | 25(56.8) | | |
| Severe | 8(18.2) | | |
| Eye involvement, n (%) | | | |
| Yes | 28 (63.6) | – | – |
| No | 16 (36.4) | | |
| Family history of cardiovascular events, n (%) | 10 (22,7) | 8 (18,2) | .635 |
| BMI, kg/m$^2$, mean ± SD | 25.7 ± 3.4 | 25.1 ± 3.0 | .255 |
| Systolic BP, mm Hg, mean ± SD | 109.5 ± 11.2 | 103.8 ± 9.2 | .020 |
| Diastolic BP, mm Hg, mean ± SD | 70.1 ± 8.6 | 66.4 ± 8.9 | .068 |

Abbreviations: ETR, erythematotelangiectatic rosacea; PPR, papulo-pustular rosacea; BMI,body mass index; BP, blood pressure.

Rosacea patients with eye involvement had a significantly greater mean CIMT than those without eye involvement (0.62 ± 0.11 vs 0.55 ± 0.07, *P* = .08; Table 4). There was no significant difference between the serum proinflammatory marker levels between the two groups, except for in the case of hs-CRP, which was significantly lower in patients with eye involvement than those without eye involvement (*P* = .040; Table 4).

### 3.3 | Correlation of the variables with disease duration and mean CIMT

No significant correlations were observed between the mean CIMT of patients with rosacea and disease duration, serum IL-6, IL-1β, TNF-α, hs-CRP, N/L ratio, P/L ratio, and MPV values. Similarly, there was no significant correlation between disease duration and serum proinflammatory markers (Table 5).

## 4 | DISCUSSION

Recently, rosacea has been associated with various systemic comorbidities, including metabolic, neurologic, psychiatric, gastrointestinal, and cardiovascular disorders. Data on the relationship between rosacea and cardiovascular disorders are controversial. In some case-control studies, it has been shown that classical cardiovascular risk factors, such as hyperlipidemia, hypertension, metabolic syndrome, family history of CVD, smoking, and alcohol consumption were more common in rosacea patients than in controls.[11,25,26] Hua et al. reported an increased risk of coronary artery disease in rosacea patients after adjusting for certain risk factors (odds ratio [OR] = 1.20 [95% confidence interval (CI), 1.14-1.26]).[11] Conversely, some studies did not observe an overall association between rosacea and CVD. A retrospective study of 4948 rosacea patients found that rosacea was not associated with increased risk of adverse cardiovascular outcomes (myocardial infarction, ischemic and hemorrhagic stroke, and death).[13] Similarly, in a case control study by Marshall et al, no significant correlation was found between rosacea and CVD or cardiovascular risk factors.[27]

Atherosclerosis is the leading cause of cardiovascular mortality and morbidity. There is growing body of evidence linking atherosclerosis to chronic inflammation. The premature and accelerated development of atherosclerotic disease in inflammatory disorders such as psoriasis vulgaris and rheumatoid arthritis has been related to endothelial dysfunction due to chronic inflammation overload and to the increased prevalence of traditional cardiovascular risk factors among

**TABLE 2** Laboratory and carotid ultrasound findings in patients with rosacea and healthy control subjects

| Variable | Rosacea, n = 44 | Control, n = 44 | *P* |
|---|---|---|---|
| Right CIMT, mm, mean ± SD | 0.59 ± 0.09 | 0.62 ± 0.10 | .144 |
| Left CIMT, mm, mean ± SD | 0.60 ± 0.10 | 0.62 ± 0.11 | .256 |
| Mean CIMT, mm, mean ± SD | 0.59 ± 0.08. | 0.62 ± 0.09 | .098 |
| Carotid plaque, n (%) | | | .645 |
| Yes | 2 (4.5%) | 3 (6.8%) | |
| No | 42 (95.5%) | 41 (94.6%) | |
| Neutrophil count, K/mL, mean ± SD | 3.8 ± 1.1 | 3.6 ± 1.5 | .215 |
| Lymphocyte count, K/mL, mean ± SD | 2.1 ± 0.7 | 2.1 ± 0.6 | .707 |
| Platelet count, K/mL, mean ± SD | 246.9 ± 67.3 | 266.5 ± 63.2 | .136 |
| NLR, mean ± SD | 2.0 ± 0.7. | 1.8 ± 0.7 | .066 |
| PLR, mean ± SD | 125.8 ± 44.3 | 135.7 ± 41.6 | .152 |
| MPV, mean ± SD | 10.5 ± 0.9 | 10.5 ± 0.9 | .773 |
| ESR, mm/first h, mean ± SD | 15.3 ± 12.6 | 14.6 ± 8.8 | .688 |
| Fasting glucose, mg/dL, mean ± SD | 93.0 ± 7.8 | 92.9 ± 6.4 | .953 |
| LDL-c, mg/dL, mean ± SD | 108.2 ± 20.0 | 104.7 ± 23.3 | .667 |
| HDL-c, mg/dL, mean ± SD | 53.2 ± .1.4 | 53.3 ± 11.5 | .977 |
| Total cholesterol, mg/dL, mean ± SD | 176.3 ± 23.5 | 175.5 ± 27.4 | .953 |
| Triglycerides, mg/dL, mean ± SD | 89.4 ± 30.5 | 87.8 ± 29.1 | .809 |
| Hs-CRP, pg/mL, mean ± SD | 26.6 ± 9.4 | 13.9 ± 2.5 | <.001 |
| IL-1ß, pg/mL, mean ± SD | 165.2 ± 25.0 | 74.4 ± 13.4 | <.001 |
| IL-6, pg/mL, mean ± SD | 194.9 ± 24.9 | 115.1 ± 20.8 | <.001 |
| TNF-a, pg/mL, mean ± SD | 246.9 ± 44.4 | 164.0 ± 31.4 | <.001 |

Abbreviations: CIMT, carotid intima-media thickness; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte; MPV, mean platelet volume; ESR, erythrocyte sedimentation rate; LDL, low-density lipoprotein; HDL, high-density lipoprotein; hs-CRP, high sensitivity C-reactive protein; IL-1β, interleukin-1 beta; IL-6, interleukin-6; TNF-α, tumor necrosis factor-alpha.

**TABLE 3** Laboratory and carotid ultrasound findings according to the rosacea subtype and disease severity

| | Rosacea subtype | | | Disease severity | | |
|---|---|---|---|---|---|---|
| Variable | ETR(n = 25) | PPR(n = 17) | *P* | Mild(n = 11) | Moderate–severe(n = 33) | *P* |
| Right CIMT, mm, mean ± SD | 0.58 ± 0.09 | 0.59 ± 0.09 | .477 | 0,56 ± 0.10 | 0.59 ± 0.08 | .166 |
| Left CIMT, mm, mean ± SD | 0.58 ± 0.11 | 0.60 ± 0.08 | .457 | 0.54 ± 0.08 | 0.62 ± 0.10 | .018 |
| Mean CIMT, mm, mean ± SD | 0.58 ± 0.09 | 0.60 ± 0.06 | .403 | 0.55 ± 0.08 | 0.61 ± 0.08 | .047 |
| Hs-CRP, pg/mL, mean ± SD | 25.9 ± 8.4 | 27.1 ± 11.3 | .599 | 26.8 ± 9.0 | 26.6 ± 9.7 | .881 |
| IL-1ß, pg/mL, mean ± SD | 166.9 ± 23.0 | 161.4 ± 28.5 | .654 | 157.1 ± 25.1 | 167.9 ± 24.8 | .980 |
| IL-6, pg/mL, mean ± SD | 195.3 ± 25.8 | 193.4 ± 24.9 | .710 | 188.2 ± 27.4 | 197.2 ± 24.1 | .424 |
| TNF-a, pg/mL, mean ± SD | 254.2 ± 41.4 | 238.4 ± 43.7 | .276 | 240.8 ± 40.1 | 249.0 ± 46.2 | .597 |
| NLR, mean ± SD | 1.85 ± 0.63 | 2.08 ± 0.71 | .356 | 1.71 ± 0.46 | 2.05 ± 0.69 | .284 |
| PLR, mean ± SD | 131.2 ± 47.4 | 118.5 ± 41.4 | .465 | 125.0 ± 40.1 | 126.1 ± 46.3 | .978 |
| MPV, mean ± SD | 10.4 ± 0.9 | 10.4 ± 1.0 | .777 | 10.3 ± 1.0 | 10.5 ± 0.9 | .342 |

Abbreviations: ETR, erythematotelangiectatic rosacea; PPR, papulo-pustular rosacea; CIMT, carotid intima-media thickness; hs-CRP, high sensitivity C-reactive protein; IL-1β, interleukin-1 beta; IL-6, interleukin-6; TNF-α, tumor necrosis factor-alpha; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; MPV, mean platelet volume.

those patients.[28-30] Rosacea is a chronic inflammatory disorder, as the dysregulation of innate and adaptive immune pathways and neurogenic inflammation seem to be driving forces in rosacea pathophysiology. In two recent studies from Turkey, rosacea patients were found to have higher CIMT and epicardial fat tissue values compared with controls.[31,32] Our study could not revalidate this finding,

**TABLE 4** Laboratory and carotid ultrasound findings in rosacea patients with and without eye involvement

| | Eye involvement | | |
|---|---|---|---|
| Variable | Yes, n = 28 | No = 16 | *P* |
| Right CIMT, mm, mean ± SD | 0.61 ± 0.08 | 0.55 ± 0.10 | .015 |
| Left CIMT, mm, mean ± SD | 0.62 ± 0.11 | 0.56 ± 0.08 | .045 |
| Mean CIMT, mm, mean ± SD | 0.61 ± 0.08 | 0.55 ± 0.07 | .008 |
| Hs-CRP, pg/mL, mean ± SD | 24.4 ± 9.2 | 30.6 ± 8.6 | .040 |
| IL-1ß, pg/mL, mean ± SD | 162.9 ± 26.4 | 169.2 ± 22.7 | .393 |
| IL-6, pg/mL, mean ± SD | 189.9 ± 27.4 | 203.8 ± 17.4 | .071 |
| TNF-a, pg/mL, mean ± SD | 248.7 ± 43.7 | 243.9 ± 47.0 | .922 |
| NLR, mean ± SD | 2.05 ± 0.71 | 1.80 ± 0.52 | .428 |
| PLR, mean ± SD | 128.1 ± 46.8 | 121.9 ± 40.8 | .742 |
| MPV, mean ± SD | 10.4 ± 1.0 | 10.5 ± 0.9 | .625 |

Abbreviations: CIMT, carotid intima-media thickness; hs-CRP, high sensitive C-reactive protein; IL-1β, interleukin-1 beta; IL-6, interleukin-6; TNF-α, tumor necrosis factor-alpha; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; MPV, mean platelet volume.

**TABLE 5** Correlation of the variables with disease duration and mean carotid intima-media thickness (CIMT)

| | Mean CIMT | | Disease duration | |
|---|---|---|---|---|
| | rho | *P* | rho | *P* |
| Hs-CRP, pg/mL, mean ± SD | −0.121 | .263 | −0.241 | .115 |
| IL-1ß, pg/mL, mean ± SD | −0.137 | .202 | 0.110 | .476 |
| IL-6, pg/mL, mean ± SD | −0.164 | .127 | −0.102 | .509 |
| TNF-a, pg/mL, mean ± SD | −0.125 | .246 | 0.151 | .327 |
| NLR, mean ± SD | 0.034 | .751 | 0.243 | .111 |
| PLR, mean ± SD | −0.063 | .561 | 0.223 | .147 |
| MPV, mean ± SD | 0.095 | .379 | 0.121 | .434 |
| Mean CIMT, mm, mean ± SD | – | – | 0.147 | .340 |

Abbreviations: cIMT, carotid intima-media thickness; hs-CRP, high sensitive C-reactive protein; IL-1β, interleukin-1 beta; IL-6, interleukin-6; TNF-α, tumor necrosis factor-alpha; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; MPV, mean platelet volume.

as mean CIMT and carotid plaque prevalence did not differ significantly between the rosacea patients and control subjects. A possible explanation of this finding could be our strict exclusion criteria for the study. We did not include any patients with any traditional cardiovascular risk factors to overcome their potential additive effect on CIMT values. However, in the previously mentioned two studies, rosacea patients were related to at least one traditional cardiovascular risk factor such as higher blood pressure or higher serum cholesterol levels compared with the control group. Our findings suggest that rosacea might not be an independent risk factor for atherosclerosis, but a higher prevalence of traditional cardiovascular risk factors in patients with rosacea could contribute to accelerated atherosclerosis. Nevertheless, future studies will be required to further clarify this finding.

IL-1β, IL-6, and TNF-α are well-established proatherogenic cytokines, and their increased production accelerates atherosclerosis by causing endothelium dysfunction, upregulating adhesion molecules and chemokines, and promoting the destabilization of atherosclerotic plaques.[33,34] The role of these cytokines in rosacea pathogenesis have also been shown in rosacea-affected skin. Skin sample analyses of rosacea patients have revealed a higher expression of genes encoding IL-1β, IL-6, and TNF-α and rosacea trigger factors, such as UV radiation and demodex mites, which lead to the increased production of these proinflammatory cytokines through TLR-2 and cathelicidin LL-37 signaling.[35-37] However, there are only a few studies investigating the serum levels of these cytokines and their results are conflicting. Hs-CRP is a very sensitive marker of systemic inflammation and is the most widely evaluated biomarker for CVD risk prediction.[38] In this study, we report higher serum IL-1β, IL-6, TNF-α, and hs-CRP levels in patients with rosacea compared with the control group. Considering that none of our patients had any concomitant systemic diseases, the high levels of these serum proinflammatory markers might suggest that inflammation in rosacea patients is not only restricted to the skin, but also that higher systemic inflammation in rosacea patients might be a possible link to rosacea-related comorbidities. A previous study reported that treatment of rosacea using oral tetracyclines reduced the risk of future cardiovascular events (OR = 0.67) and this preventive effect was linked to its systemic antiinflammatory properties.[39]

Although the same cellular pathways play a role in the pathogenesis of both subtypes of ETR and PPR, it has been suggested that at the tissue level, an inflammatory threshold must be reached for papule and pustule formation.[40] In addition, higher expression of inflammatory mediators has been reported in PPR in various studies.[35,41] In our study, the serum proinflammatory cytokine and marker levels did not show any important difference between the ETR and PPR subtypes, which led us to the conclusion that the systemic inflammation level in rosacea patients does not seem to be dependent on disease subtype. In line with our findings, in another recent study, serum oxidative stress and antioxidant capacity levels did not differ between rosacea subtypes.[9]

In the present study, rosacea patients with moderate-severe disease had a higher mean CIMT than patients with mild disease, even

though the serum proinflammatory cytokine and marker levels did not differ between groups. In a case-control study by Rainer et al, rosacea was associated with numerous systemic comorbid diseases in a skin severity-dependent manner, and compared with mild rosacea, moderate to severe rosacea was significantly associated with CVD. Consistent with this finding, subclinical atherosclerosis was associated with disease severity in our study.

Immune system dysregulation and inflammation also play an important role in ocular rosacea etiopathogenesis. In some studies, various inflammatory marker levels were found to be higher in the tears of patients with ocular rosacea. However, Topcu-Yılmaz et al found that serum IL-1a, IL-6, and TNF-α levels did not differ between rosacea patients with and without ocular disease. Similarly, in our cohort, serum proinflammatory cytokine levels were not significantly different between patients with or without ocular involvement. However, we found higher mean CIMT values in patients with ocular involvement. This fact suggests that ocular involvement could be an important risk factor for subclinical atherosclerosis among rosacea patients.

The limitations of our study include an overall small size sample, as well as limitations that are inherent to a cross-sectional design, mainly the inability to establish probable causality. Another limitation could be the lack of investigation into other subclinical atherosclerosis markers like the flow-mediated vasodilation of the brachial artery or epicardial fat tissue.

In conclusion, we have showed that patients with rosacea have higher serum proinflammatory marker levels, although the inflammation level was not dependent on rosacea subtype or disease severity. In the absence of other traditional cardiovascular risk factors, rosacea does not seem to affect mean CIMT values. However, patients with moderate to severe disease and patients with ocular involvement were associated with an increased risk of subclinical atherosclerosis. Based on these findings, we suggest that patients with rosacea be screened for traditional cardiovascular risk factors and CVD according to the current age-based recommendations. Additional attention may be of importance in particular subgroups, such as patients with severe disease or with ocular involvement. Further studies with larger cohorts are needed to clarify the relationship between rosacea and CVD and to determine whether controlling disease activity with any specific treatment has a preventive effect on cardiovascular events in rosacea patients.

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## CONFLICT OF INTEREST

The authors declare no conflicts of interest.

## AUTHOR CONTRIBUTIONS

Sümeyre Seda Ertekin, Mehmet Salih Gürel, Eray Metin Güler: Conception and design of the work; Sümeyre Seda Ertekin, Eray Metin Güler, Melis Baykara Ulusan: Data collection; Sümeyre Seda Ertekin, Mehmet Salih Gürel, Abdurrahim Koçyiğit: Data analysis and interpretation; Sümeyre Seda Ertekin: Drafting article; Mehmet Salih Gürel, Ayşe Esra Koku Aksu: Critical revision of the article.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available to privacy or ethical restrictions.

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