Dermatology Practical & Conceptual

Serum Endoglin and Endocan Levels in Rosacea and Their Association with Cardiovascular Risk Factors: A Case-Control Study

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ABSTRACT

Introduction: Rosacea, a chronic skin disease characterized by facial redness, is believed to involve inflammation and angiogenesis in its pathogenesis. Endocan and endoglin, biomarkers associated with vascular and inflammatory processes, might play roles in rosacea and cardiovascular comorbidities.

Objectives: This study aimed to assess serum levels of endocan and endoglin in individuals with rosacea and the function of these biomarkers in indicating comorbidities associated with rosacea.

Methods: A total of forty-four patients diagnosed with rosacea and thirty-three healthy controls were included in this case-control study. The endocan and endoglin levels in serum samples from both groups were measured.

Results: No significant difference in endocan and endoglin levels was observed between the patient and control groups. However, their levels were associated with various clinical features, including symptom and disease severity. A notable association was identified between waist circumference, body mass index, and endoglin levels. However, this association was not evident for endocan.

Conclusions: This study suggests endocan and endoglin may play roles in rosacea pathogenesis, with endoglin potentially associated with increased cardiovascular risk.

Introduction

Rosacea is a chronic inflammatory skin disease typified by facial redness, telangiectasias, occurrence of papulopustular lesions, and phymatous changes. It predominantly affects females and individuals with Fitzpatrick skin types 1 or 2 [1-7]. The histopathology of rosacea is generally nonspecific, hence the diagnosis is predominantly based on clinical observations. In pathology, findings such as spongiosis, perivascular lymphohistiocytic infiltration, dilated capillaries, and solar elastosis are commonly observed [8]. Immunologically, various factors such as T helper (Th) 1 and Th17 lymphocytes, tumor necrosis factor (TNF) alpha, inflammasome complex, interleukin (IL)-17A, vascular endothelial growth factor (VEGF), toll-like receptor (TLR)-2 expression, and cathelicidin molecules have been associated with the pathophysiology of rosacea [9-22].

Endoglin (CD105) acts as a coreceptor for ligands of the transforming growth factor (TGF)-beta family and has a molecular weight of 180 kilodaltons (kDa). Endoglin is predominantly secreted by activated endothelial cells and plays a crucial role in angiogenesis, closely associated with the VEGF molecule [23-28].

Endocan is a proteoglycan with a dermatan sulfate structure [29]. It is secreted from the human vascular endothelium and is also found freely circulating in the bloodstream [30]. It participates in diverse cellular mechanisms, including cell proliferation, migration, angiogenesis, and inflammation [29,31,32].

The correlation between these molecules and concurrent conditions such as diabetes, coronary artery disease, metabolic syndrome, and hypertension has been seen in numerous research studies [28,30,31,33].

Objectives

The purpose of this research was to investigate the involvement of the molecules endocan and endoglin in the pathogenesis of rosacea. Furthermore, this study assessed the potential of endocan and endoglin levels as biomarkers for predicting cardiovascular disease risk in patients with rosacea.

Methods

Study Design

This 16-week case-control study included 44 patients in the patient group, aged 28-74 years, who were diagnosed with rosacea based on the 2017 National Rosacea Society Expert Committee criteria [34]. The control group consisted of 33 adults who were examined for dermatological diseases other than rosacea. Exclusion criteria included individuals under 18 years of age, pregnant or lactating women, active infections, concomitant inflammatory skin diseases, smoking, anemia, obstructive lung disease, atrial fibrillation and arrhythmia, anomalies in thyroid function tests, left ventricular dysfunction, malignancy, coronary artery disease, valvular heart disease, diabetes, arterial hypertension, renal-hepatic insufficiency, obesity, hyperlipidemia, autoimmune diseases, individuals who received systemic treatment for rosacea within the previous six months, and individuals taking drugs such as amlodipine and valsartan that could affect endocan levels [33].

Study Protocol

The study was conducted in accordance with the principles outlined in the Helsinki Declaration. The study protocol was approved by the local ethics committee (Mersin University) on 30 September 2020, under decision number 663. Prior to the commencement of the study, all patients were adequately informed about the research and provided their written informed consent.

Data Collection

Demographic data, height, weight, waist circumference, body mass index (BMI), alcohol and smoking history, and presence of metabolic syndrome were obtained from the patients and the control group participants. Systolic and diastolic blood pressures (SBP, DBP) were measured by the same investigator using a mercury sphygmomanometer after a 20-minute rest in a seated position. Hypertension was defined as SBP ≥140 mmHg and DBP ≥90 mmHg.

Clinical Assessment

In this study, we evaluated various clinical aspects in the patient group, including skin phototype, rosacea subtype, symptoms, triggering factors, flushing, persistent erythema, papulopustular lesion count, telangiectasia, phymatous changes, edema, extra facial involvement, ocular symptoms, and disease severity. We also examined the presence of Demodex mites and assessed past and current rosacea treatments. Parameter severity scoring was performed according to the grading system established by the National Rosacea Society in 2004: 0 – absent, 1 – mild, 2 – moderate, 3 – severe [35] . In this study, Demodex mites were detected using the standardized skin surface biopsy method. Cases in which more than five Demodex mites were observed in the 1 cm^2 area were classified as positive for Demodex infestation [36].

Measurement of Biochemical Measurements

Peripheral venous blood samples were taken from the patient and control groups in Vacutainer tubes without additives after a 12-hour fast between 07:00-08:00 am, without

stasis, following at least 20 minutes of rest. Care was taken to ensure that participants did not use medications, smoke, or consume alcohol before blood collection. After 15 minutes, the blood samples were centrifuged at 4000 rpm for 10 minutes. After centrifugation, serum aliquots were stored at -80° C until analysis. Endocan, endoglin, insulin, glucose, total cholesterol, high-density lipoprotein (HDL), triglyceride (TG), and C-reactive protein (CRP) levels were measured on the same day.

Insulin levels were measured by chemiluminescence immunoassay, glucose and total cholesterol levels by enzymatic assays, HDL and TG levels by enzymatic calorimetric assays, CRP levels by an immunoturbidimetric assay, and sedimentation levels by the Westergren method. Low-density lipoprotein (LDL) levels were calculated using the Friedwaid formula. Insulin resistance was assessed utilizing the homeostasis model assessment of insulin resistance (HOMA-IR), employing the following formula: HOMA-IR = fasting insulin level (uIU/mL) × fasting glucose level (mg/dL) /405. A HOMA-IR value exceeding 2 was indicative of insulin resistance.

On the analysis day, the serum samples stored at -80° C were brought to room temperature, and serum endocan (Bioassay Technology Laboratory, E3160Hu) and endoglin (Bioassay Technology Laboratory, E3407Hu) levels were measured according to the manufacturer's recommended protocol using the DSX 4-Plate automated enzyme-linked immunosorbent assay (ELISA) Processing System. The concentration of each sample was calculated using the equation and curve drawn with optical density (OD) values corresponding to known standards for each analysis.

Statistical Analysis

The analyses were performed using Statistica v.13.3.1 software. A p-value of <0.05 was considered statistically significant. The normal distribution of variables was assessed using the Shapiro-Wilk test. Normally distributed continuous variables were summarized as mean ± standard deviation, and non-normally distributed variables were summarized as median [25th-75th percentile]. Categorical variables were summarized as numbers and percentages. independent samples t-test was used for group comparisons when the assumptions were met; otherwise, the Mann-Whitney U test and Kruskal-Wallis test were used for multiple group comparisons, followed by the Dunn test as the post hoc test. Spearman's correlation coefficient was used to investigate the relationship between continuous variables, while the chi-squared test and Fisher's exact test were used to investigate the relationship between categorical variables when the expected frequency was less than five and the percentage was greater than 20%. Bonferroni correction was applied for pairwise comparisons.

Results

The study included 44 rosacea patients and 33 individuals in the control group. The mean age of the patients was 45.05 ± 10.9 years, whereas the mean age of the control group was 45.21 ± 8.70 years. Among the patients, 77.3% (n=34) were female, while 22.7% (n=10) were male. No significant difference was observed in sex and age distribution between the control and patient groups (P=1, P=0.983, respectively). The mean body mass index of the patient group was 26.8 ± 3.8 kg/m², and the mean waist circumference was 92.07 ± 12.1 cm. The two groups had no significant differences in BMI and waist circumference (P=0.735, P=0.336, respectively). Regarding HDL, LDL, SBP, total cholesterol, CRP, TG, insulin, HOMA-IR, fasting blood glucose, and metabolic syndrome, no statistically significant variance was noted between the patient and control groups (P=0.73, P=0.589, P=0.13, P=0.69, P=0.32, P=0.26, P=0.35, P=0.22, P=0.45, P=1, respectively). The demographic and clinical characteristics of rosacea patients and healthy controls are presented in Table 1, and the significant biochemical parameters in rosacea patients and the control group are presented in Table 2.

Fitzpatrick skin type II was observed in 23% of the patients, type III in 63%, and type IV in 14%. A family history of rosacea was present in 43.2% of the patients. The average disease duration was 5.6 ± 4.53 years. Among the patients, the most common subtype was erythematotelangiectatic (ET) rosacea (61.4%), followed by papulopustular (PP) rosacea (34.2%), and phymatous rosacea (4.4%). Disease severity assessment revealed that 20.5% (n=9) of the patients had mild disease, 41% (n=18) had moderate disease, and 38.5% (n=17) had severe disease. Demodicosis was detected in 63.6% of the patients.

The median level of endocan in patients was 176 ng/L, with a mean of 371.1 ng/L and in the control group; the median value was 194 (142-692) ng/L with a mean of 280.7 ng/L. We did not find any difference between these groups (P=0.765). The median level of endoglin in patients was 5.4 ng/mL, with a mean of 8.6 ng/mL; in the control group, the median value was 6.8 ng/mL, with a mean of 8.6 ng/mL. No discernible difference was observed between the groups (P=0.111). No statistically significant correlation was found between age or sex with endocan and endoglin levels (P=0.154, P=0.382, P=0.836, P=0.286, respectively). The levels of endoglin and endocan in the patient and control groups are shown in Figures 1A and 1B.

No significant association was identified between HDL, LDL, SBP, DBP, total cholesterol, CRP, TG, insulin, HOMA-IR, or fasting blood glucose levels with endocan and endoglin.

Statistically significant relationships were identified between waist circumference and BMI and levels of endoglin

Table 1. Demographic and clinical characteristics of rosacea patients and healthy controls.

Characteristics	Control Group n[a]=33	Rosacea Group n[a]=44
Female, n (%)	25 (75.7%)	34 (77.3%)
Male, n (%)	8 (24.3%)	10 (22.7%)
Age, years, mean (SD)	45.21 (8.70)	45 (10.9)
BMI[b], mean (SD), kg/m^2	27.03 (3.77)	26.8 (3.8)
Weight, mean (SD) , kg	75.21 (12.61)	73.3 (12.5)
Waist circumference, mean (SD), cm	89.48 (11.74)	92 (12.1)
Family comorbidity, n(%)	27 (81.8)	36 (81.8)
Disease duration, years, mean (SD)	-	5.6 (4.)
Subtype, n(%)	-	
Erythematotelangiectatic	-	27 (61.4)
Papulopustular	-	15 (34.2)
Phymatous	-	2 (4.4)
Disease Severity	-	
Mild n(%)	-	9 (20.5)
Moderate n(%)	-	18 (41)
Severe n(%)	-	17 (38.5)

[a]: Number of samples; [b]: body mass index.

Table 2. Laboratory Values in the Patient and Control Groups.

	Control group, n[a]=33			Patient group, n[a]=44			
	Median	*Min*	*Max*	*Median*	*Min*	*Max*	*p*[b]
CRP[c]	2	1	13	3	1	15	0.26
TG[d]	110	45	483	121	47	414	0.27
Insulin	6.8	2.3	23	7.5	3	38	0.41
HOMA-IR[e]	1.7	0.5	5.8	1.9	0.7	9.3	0.28
FBG[f]	98	77	116	99.5	82	155	0.50

[a]: number of samples; [b]: values of significance with difference of each group; [c]: C reactive protein; [d]: triglyceride; [e]: homeostasis model assessment of insulin resistance. [f]: fasting blood glucose.

(*P*=0.005, *P*=0.014, respectively). No substantial association was found between rosacea subtypes and levels of endocan and endoglin (*P*=0.730, *P*=0.527, respectively).

A notable correlation was observed between the presence of symptoms (*P*<0.001, *P*<0.001), erythema severity (*P*<0.001, *P*=0.004), disease severity (*P*<0.001, *P*=0.007) and endocan and endoglin levels. The intensity of telangiectasia was found to have a strong correlation with endocan levels (*P*=0.007).

A significant association was also noted between endoglin levels and the occurrence of flushing attacks (*P*=0.003), the number of papulopustular lesions (*P*=0.045) ,and demodicosis (*P*=0.040). The levels of endocan and endoglin in mild, moderate, and severe rosacea patients are shown in Figures 2A and 2B.

Conclusions

Endocan is a proteoglycan being investigated for its role in many inflammatory diseases where angiogenesis is increased, such as coronary artery disease, hypertension, and psoriasis [29,31,37,38]. The endoglin molecule also plays a role in many angiogenesis-related pathways where VEGF, TGF-beta, and similar angiogenic molecules are involved [23,39]. Our study explored the association between rosacea and endocan and endoglin molecules, which are known to play significant roles in pathways such as angiogenesis, vasodilation, and inflammation. We also investigated the relationship between these molecules and cardiovascular risk factors [9,14].

In this study, we hypothesized that in rosacea patients with high levels of endocan and endoglin molecules,

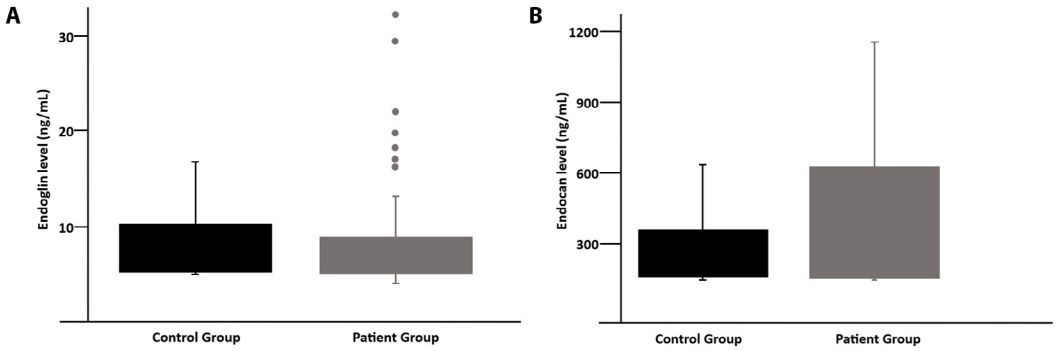

Figure 1. Endoglin levels in the patient and control groups (a) and endocan levels in the patient and control groups (b).

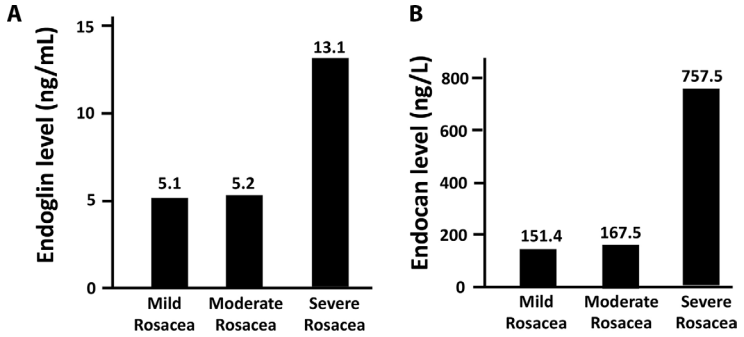

Figure 2. Level of endoglin in mild, moderate, and severe cases of rosacea (a) and level of endocan in mild, moderate, and severe cases of rosacea (b).

VEGF-mediated angiogenesis, inflammation, and increased vasodilation through molecules such as TNF-alpha and IL-17 could lead to more severe symptoms, more severe telangiectasia, persistent erythema, and flushing attacks. The study undertaken by Buhl et al. demonstrated the involvement of immune dysregulation in the pathogenesis of rosacea, with Th1 and Th17 cells, TNF-alpha, IL-1, IL-6, IL-8, IL-17 cytokines, increased TLR-2 expression, MMPs, and the inflammasome complex playing crucial roles [11]. A study by Schwab et al. also demonstrated the importance of molecules such as VEGF and LL-37 in angiogenesis, as well as factors like cathelicidin, nitric oxide (NO), and pro-inflammatory pathways in vasodilation in the development of rosacea [21]. Endocan, on the other hand, is a vital proteoglycan involved in both angiogenesis and inflammation, and these mechanisms have been investigated in numerous studies. Sarrazin et al. showed that its expression in vascular endothelial cells is regulated by several cytokines, including TNF-α, VEGF, and fibroblast growth factor (FGF)-2 [29]. The role of endocan in cardiovascular comorbidities has also been the subject of many studies. The study by Balta et al. found that endocan serves as an emerging inflammatory marker among atherosclerotic patients and could potentially serve as a valuable predictor of cardiovascular events [37]. In contrast to these studies, our research did not identify an association between endocan levels and metabolic parameters such as lipid levels, fasting blood glucose, or insulin resistance. This result could be attributed to the selection of patients and control group without comorbidities and not using systemic medication. To our knowledge, only one study has investigated the relationship between endocan and rosacea. That study reported that elevated endocan levels were detected in patients with rosacea, suggesting a potential association with increased levels of VEGF [40]. According to our findings, endocan alone is not causative in the development of rosacea, but its levels increase in severe cases. It is not possible to definitively state from the existing literature that endocan is involved in the pathogenesis of rosacea.

In a study conducted by Sánchez-Elsner et al., it was reported that hypoxia and TGF-beta release increase the secretion of endoglin and VEGF [41]. In another study, by Furuya et al., VEGFR-2 and endoglin were identified as markers for tumor-derived endothelial cells in investigating molecules related to tumor neovascularization. Endoglin is typically released at low levels from normal endothelium, but its levels in serum increase during embryogenesis, inflammatory diseases, and tumorigenesis [42].

Research conducted by Wladis et al. demonstrated elevated endoglin levels in ocular rosacea, indicating heightened

levels in cutaneous arterioles, which are associated with inflammation and vascular remodeling [43]. The association between endoglin, facial rosacea, and demodicosis has not been investigated in any study to date. Given these observations and our findings, we hypothesize that the endoglin molecule may contribute to the development of telangiectasia, flushing, and erythema observed in rosacea. Casas et al. performed a study that found a significant increase in the density of Demodex folliculorum in patients with rosacea as well as marked elevations in the levels of TNF-alpha, IL-6, IL-8, and VEGF [22]. We theorized that the increased endoglin level in Demodex-positive patients might be associated with an enhanced inflammatory response, but this relationship was not confirmed in our study with endocan.

Beyond diseases associated with angiogenesis, endoglin is implicated in various systemic diseases. Li et al. observed that high levels of endoglin are associated with high SBP, DBP, and BMI and are correlated with carotid intima-media thickness [44]. In our study, an association was found between endoglin, increased waist circumference, and BMI, corroborating findings from other studies. Endoglin may be a parameter indicating the development of comorbidities in rosacea.

In the present study, levels of endocan and endoglin were not investigated in tissue biopsy samples, which is a limitation. There are many different molecular pathways that could affect serum levels of endocan and endoglin. For a more specific conclusion, future research should examine the difference in levels of these molecules between rosacea-affected tissue and healthy tissue.

Other limitations of our study include the examination of serum endocan and endoglin levels performed on a limited number of patients with rosacea, the inability to conduct ocular examinations on the participants, and restriction to a single center.

In conclusion, elevated serum levels of endocan and endoglin have been linked to the progression of rosacea to a more severe stage, characterized by increased telangiectasia and intense erythema and severe symptoms attributed to heightened inflammation and angiogenesis. We believe that these molecules could serve as potential target molecules for future rosacea treatments. To better understand the role of endocan and endoglin molecules in the pathogenesis of rosacea, larger-scale studies involving more patients and control participants are needed. Additionally, endoglin levels could be utilized to identify the risk of cardiovascular diseases in rosacea groups. Furthermore, in future studies, repeated measurements of endocan and endoglin before and after treatment could provide us with information regarding the treatment's antiangiogenic and anti-inflammatory efficacy.

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Ethical Approval: The study protocol was approved by the local ethics committee (Mersin University) on September 30, 2020, under decision number 663.

Ethics Statement: The patients in this manuscript have given written informed consent to the publication of their case details.

Patient Consent for Publication Statement: All patients were adequately informed about the research and provided their written informed consent.

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