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Elevated Serum Endocan Levels in Patients with Rosacea: A New Therapeutic Target?

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Abstract

Background:

Rosacea is a chronic inflammatory skin disease whose etiopathogenesis is still unknown. Previous studies have shown a relationship between certain inflammatory disorders and serum endocan levels. Endocan (previously known as endothelial cell-specific molecule 1) might play a role in the pathogenesis of various inflammatory diseases.

Aims and Objectives:

Our study aimed to evaluate serum endocan levels in patients with rosacea to investigate the association of endocan with the demographic data.

Materials and Methods:

The study recruited individuals aged ≥18 years who voluntarily agreed to participate in the study. The participants included 37 women (mean age: 48.29 ± 12.08 years) and 13 men (mean age: 52.23 ± 13.34 years) diagnosed with rosacea, and 37 women (mean age: 49.18 ± 16.6 years) and 13 men (mean age: 53.69 ± 11.30 years) selected as controls. Both groups were matched according to age and sex. The rosacea diagnosis was based on clinical examination findings, and serum endocan levels were measured using the method of enzyme-linked immunosorbent assay (ELISA). The statistical significance of the data was determined by the Mann–Whitney *U* test, and a value of $P < 0.05$ was considered statistically significant.

Results:

Serum endocan levels differed significantly between the patients with rosacea and the control group ($P < 0.05$).

Conclusion:

Circulating endocan might be a new marker related to disease progression in patients with rosacea. Further investigation is needed to determine whether endocan levels could become a new therapeutic target in rosacea, a disease that still cannot be fully cured.

Key Words: *Endocan*, *ESM-1*, *inflammation*, *rosacea*

Introduction

Rosacea is a common skin disease that can develop in adults of all ethnicities but occurs more often in people with fair skin (Fitzpatrick skin phototypes 1 and 2). Fixed centrofacial erythema, phymatous changes, papules, pustules, flushing, telangiectasia, burning and stinging, edema, and a dry appearance characterize skin findings. Ocular abnormalities can also occur. Although the pathogenesis of rosacea is not fully understood, factors such as innate immune system disorders, inflammatory reactions to cutaneous microorganisms, exposure to ultraviolet radiation, and vascular hyperreactivity have been identified as potential contributing factors.[1]

Endocan (formerly known as endothelial cell-specific molecule 1 [ESM-1]) is a protein that in humans is encoded by the *ESM1* gene[2] and is mainly expressed by endothelial cells in lung and kidney tissues and the vascular endothelium. In 2001, Bechard *et al*.[3] characterized the protein as dermatan sulfate proteoglycan, and it has been known as endocan since then. Endocan can inhibit leukocytes that bind to the vascular endothelium and promote angiogenesis. Endocan might therefore play a role in the pathogenesis of various inflammatory diseases.[4]

Increased serum endocan levels in correlation with disease activity are observed in chronic systemic inflammatory dermatoses such as psoriasis and Behçet's disease.[5,6] Previous studies have reported that serum endocan levels in patients with sepsis are related to disease severity[7] and that endocan levels in renal allografts might reflect the degree of endothelial cell damage.[8] In our study, we aimed to investigate serum endocan levels in patients with rosacea, given that endocan plays an important role in the pathogenesis of rosacea characterized by chronic systemic inflammation.

Materials and Methods

Study design

Our study was approved by the Clinical Research Ethics Committee of XXXXXXX University, (decision date: 24 July 24, 2019; number: 14-02) and was supported by the XXXXX Scientific Research Commission with an independent research project (code: TSA-2020-3300). The study recruited individuals aged ≥18 years who voluntarily agreed to participate in the study. The participants were followed by the Dermatology and Venereal Diseases Polyclinic for 2–3 months. The participants included 37 women (mean age: 48.29 ± 12.08 years) and 13 men (mean age: 52.23 ± 13.34 years) diagnosed with rosacea, and 37 women (mean age: 49.18 ± 16.6 years) and 13 men (mean age: 53.69 ± 11.30 years) selected as controls. Both groups were matched according to age and sex. The exclusion criteria were as follows: (1) refusal to participate in the study, (2) use systemic therapy to treat rosacea, (3) presence of arterial hypertension, inflammatory diseases, diabetes mellitus, metabolic syndrome, or coronary artery disease, (4) smoking, (5) any kind of abnormality in the thyroid function tests, (6) presence of anemia, (7) local or systemic infection, (8) kidney or liver dysfunction (creatinine >1.5 mg dL and aspartate or alanine aminotransferase activity more than twice the upper limit of normal, respectively), (9) known malignancy, and (10) use of any drug that might interfere with the endocan measurements. Informed consent was obtained from all participants before starting the study. Potential cutaneous manifestations of rosacea; include persistent midface redness, phymatous skin changes, papules, pustules, flushing, telangiectases, burning or stinging sensation, cutaneous edema, and dryness. In most patients, it is necessary to diagnose rosacea and other disorders that may resemble rosacea (in the differential diagnosis of papulopustular lesions; acne vulgaris, Topical corticosteroid-induced acneiform eruptions, perioral dermatitis, Keratosis pilaris rubra faceii, and centrofacial erythema; Sun-damaged skin, Acute cutaneous lupus erythes)., Dermatomyositis, Seborrheic dermatitis, and other causes of

flushing) clinical evaluation is sufficient. The rosacea diagnosis was based on clinical examination findings, and serum endocan levels were measured using the method of enzyme-linked immunosorbent assay (ELISA). The results are presented in pg/mL, and the statistical analysis was performed to determine intergroup statistical significance, and determining group distributions performed correlation tests.

Analysis of endocan levels

The analyses were based on the sandwich ELISA principle. Standards or samples were bound to the target antigen capture antibody in wells on the microplate. Unbound parts were removed by washing. An avidin–horseradish peroxidase (HRP) conjugate binding to biotin was added following the procedure in the kit. Unbound avidin–HRP conjugate was removed by washing. Washing and incubation procedures were repeated in intermediate steps. We then observed the color development. We added a stop solution to terminate the color development reaction and measured the optical density (OD) of the standards and samples in the microplate at a wavelength of 450 nm ± 2 nm. We generated a standard OD graph using known antigen concentrations. We then compared the OD of the unknown sample to the standard graph to determine the antigen concentration. Endocan (MYBIOSOURCE-MBS771324 Human ESM-1/Endocan ELISA Kit 96 Tests) analyses were performed using the procedure specified in the kit datasheet. The results were expressed in pg/mL.

Statistical analysis

For the statistical analysis, we used the Statistical Package for the Social Sciences (SPSS) software program, version 19.0 (IBM, New York), using numbers, percentages, means, standard deviations, medians, and ranges to present the descriptive data. We used the Chi-squared test to compare the categorical variables and the Mann–Whitney *U* test to compare the variables that were not normally distributed. We evaluated the correlation of the variables that were not normally distributed using a Spearman correlation analysis. For statistical significance, we accepted $P < 0.05$.

The number of participants included in the groups in the study was determined by performing a power analysis. Considering previous studies, the rates of patient and control groups were compared. In order to make a decision with 95% confidence, 0.05 was chosen for a type I error and 0.20 for a type II error. Therefore, the strength of the test was determined to be 80%. Accordingly, to obtain meaningful statistical results and the minimum number of subjects per group was determined to be 30 so that the intergroup ratio could be at least 30%. In order to reduce the error rate and to interpret the results correctly, the number of subjects in the patient and control groups was determined as 50.

Results

The mean ages of the patients with rosacea and the control group were 50.26 ± 25.34 years and 51.43 ± 13.99 years, respectively. Table 1 shows the clinical subtypes of the patient group. The median serum endocan levels were 35.26 pg/mL (range: 35.26–171.34) in the patients with rosacea and 21.02 pg/mL (range: 14.42–31.14) in the control group (P = 0.000) [Table 2]. When we analyzed the endocan levels of the rosacea group by age and sex, we observed a statistically significant difference for the male patients with rosacea (P = 0.000) [Table 3].

Discussion

Rosacea is a chronic, recurrent, inflammatory skin disease that involves the central part of the face. There are two classifications of rosacea based on “pre-created” clinical subtypes (erythematotelangiectatic, papulopustular, phymatous, and ocular) or a patient-specific analysis of the rosacea phenotype.[9,10] The exact pathogenesis of the disease is still not fully understood; however, individuals with a family history of rosacea (a suggested risk factor is a polymorphism of the vascular endothelial growth factor (*VEGF*) gene [+405C/G]) might be more likely to develop the disease.[11] However, rosacea might have a multifactorial etiology with a genetic predisposition. Innate immune system dysfunction could contribute to the development of chronic inflammation and vascular abnormalities in rosacea.[12] Triggering factors (such as ultraviolet rays, heat, spices, alcohol, microbes, psychosocial stress, and skin barrier disorder) can induce neurovascular dysregulation in the innate and adaptive immune system, thereby initiating or aggravating the rosacea. Triggers might lead to the release of various mediators from keratinocytes (e.g., VEGF), neurons, endothelial cells, fibroblasts, mast cells, macrophages, and T-helper-1 and T-helper-17 cells, resulting in the emergence of rosacea lesions.[13]

Sun exposure is considered an exacerbating factor for rosacea, given the disease's predominant distribution in chronically sun-exposed areas, solar elastosis findings in skin biopsy specimens, and the more frequent occurrence of the disease in fair-skinned individuals. Various theories have been proposed regarding the mechanisms by which sun exposure can promote rosacea. Ultraviolet B radiation has been shown to induce skin angiogenesis in mice and can stimulate the secretion of VEGF and the fibroblast growth factor from keratinocytes.[14] Ultraviolet radiation can also promote the production of harmful reactive oxygen species and activation of the innate immune system.[12]

Endocan is a dermatan sulfate molecule secreted by endothelial cells that plays a key role in vascular inflammation. In addition to lung, skin, and adipose tissue, endocan is expressed in the microvascular endothelial cells of coronary and pulmonary arteries. Endocan plays a role in regulating biological cell processes such as adhesion, migration, and proliferation, with the pathogenesis of various malignancies and inflammatory diseases.[15] Endocan secretion is regulated by growth factors such as various inflammatory cytokines (interleukin-1), tumor necrosis

factor-alpha, and VEGF. The endocan expression has been reported to be highly upregulated in the presence of proangiogenic molecules such as VEGF-A and VEGF-C, which are important mediators that play a role in inflammation, metabolic events, angiogenesis, lymphangiogenesis, and cancer progression.[16,17]

The mechanisms responsible for endocan release are not fully understood; however, the protein can directly affect the function of lymphocyte function-associated antigen-1, a transmembrane glycoprotein. Endocan might therefore play a role in regulating leukocyte extravasation in inflammatory regions.[18] Endocan is expressed by vascular endothelial cells, an expression induced by VEGF-A and VEGF-C, which indicates that endocan is a direct target of VEGF and a new mediator of angiogenesis. Plasma endocan expression is also correlated with the expression of other proangiogenic factors such as vascular endothelial growth factor-A (VEGF-A) and vascular endothelial growth factor-C (VEGF-C), which play a role in the development of vascular endothelial damage.[19] VEGF-induced serum endocan levels are therefore associated with chronic inflammation. Free oxygen radicals and pro-inflammatory cytokines produced under chronic inflammation conditions are known to induce angiogenesis, insulin resistance, lipid metabolism, and epidermal hyperproliferation.[20]

Endocan levels have been evaluated in numerous inflammatory dermatoses. For example, endocan levels were examined in lesional skin and serum in a study conducted in patients with atopic dermatitis. A study reported increased endocan expression in lesional skin associated with the development of atopic dermatitis through angiogenesis and decreased serum endocan levels associated with increased leukocyte uptake in atopic dermatitis.[21] In Behçet's disease and psoriasis, high serum endocan levels have been reported in correlation with disease activity.[5,6]

In our study, we found that serum endocan levels were significantly higher in patients with rosacea. A study on patients with sepsis reported that blood endocan levels were associated with disease severity and poor prognoses[22]; however, the exact role of blood endocan levels in disease severity is unknown in patients with rosacea. We found that the serum endocan levels were higher in the male patients with rosacea than in the female patients, a finding that might be related to the suggested hypotheses as to why the coronavirus disease 2019, a current worldwide health crisis, is more common and causes more death in men than in women.[23] Given that the X chromosome contains a high density of immune-related genes and is associated with sex-specific inflammatory responses, men might be more prone to inflammatory diseases through the inducing of a weaker innate and adaptive immune response.[24]

In conclusion, and according to our hypothesis, the role of endocan in the pathogenesis of rosacea might be related to an increased VEGF production which is a strong proangiogenic factor released by keratinocytes that have the effect of triggering factors. VEGF-A and VEGF-C increase endocan expression, and inflammatory pathways are activated by an increase in endocan levels.

Although our study included a limited number of patients, our results suggest that larger case-control studies with extended follow-up evaluations are warranted, given that endocan levels might be a new therapeutic target. We believe our study supports the studies conducted to date and sheds light on current research.

Limitation

Our study does not have a sample size to evaluate all subtypes of rosacea. In particular, the number of patients in the phymatous rosacea group, which is one of the subtypes of rosacea, was very low. Future multicenter clinical and laboratory studies with larger sample sizes will enable us to better understand the relationship between rosacea and its subtypes with serum endocan levels.

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Conflicts of interest

There are no conflicts of interest.

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Figures and Tables

Table 1

Disease characteristics of rosacea patients

	Female (*n*)	Male (*n*)
Sub-type of Rosacea		
Papulopustular	11 (29.7%)	4 (30.8%)
Erythematotelengiectatic	23 (62.2%)	5 (38.5%)
Phymatosis	3 (8.1%)	4 (30.8%)

Table 2

Comparison of changes serum Endocan levels of Rosacea and control groups (pg/mL)

Serum Endocan	Mean±SD	Median	Min	Max	*P*
Control	20.79±3.61*	21.02	14.42	31.14	0.000
Rosacea	47.38±33.22[a]	35.26	25.15	171.34	0.000

The groups indicated by “a” is statistically different compared to the groups with “*”, Mann-Whitney U (Z=–7.43, P=0.000)

Table 3

Age and endocan level analysis of groups by gender

	Female (*n*)	**Male (*n*)**	**Female (Age)**	**Male (Age)**	**Female Endocan pg/mL**	**Male Endocan pg/mL**	***P***
Rosacea	37 (74%)	13 (26%)	48,29±12.08	52.23±13.34	42.94±21.47*	63.45±58.79	0.000*
Control	37 (74%)	13 (26%)	49.18±16.69	53.69±11.30	20.64±3.79	21.21±3.18	0.650

*Frequency and column percentage (%). *Independent *T* test used for analysis of mean and standard deviation value of genders in groups, The difference between females and males is statistically significant in Rosacea group *P*=0.000