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The Relationship of Endocan to Disease Severity in Psoriasis: Effect of Endocan on VGEF, CXCL12 and NGF Levels

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Introduction: Psoriasis is a chronic disease accompanied by angiogenesis and inflammation, which significantly affects patients' quality of life. Its pathophysiology has not been fully elucidated. Endocan, VEGF, CXCL12, and NGF are molecules involved in inflammation and angiogenesis. There is a restricted size of studies investigating the relationship of these molecules with psoriasis. The study aims to determine the levels of endocan, VGEF, CXCL12, and NGF in psoriasis patients, identify the relationship of these parameters with illness intensity and define the correlation between serum endocan level and VGEF, CXCL12, and NGF.
Materials and Methods: In this study, endocan, VGEF, CXCL12, and NGF levels were determined in the serum of 100 healthy persons and 94 psoriasis patients using the ELISA method and compared with the control group. Illness violence was grouped with the Psoriasis Area and Severity Index (PASI); Endocan, VGEF, CXCL12, and NGF levels were compared according to disease severity. Correlation analysis was performed between endocan level and VGEF, CXCL12, and NGF in psoriasis.
Results: Endocan, VGEF, CXCL12, and NGF levels were high in psoriasis. The severity of the disease increased; the serum levels of these parameters increased. A moderate positive correlation was found between Endocan and CXCL12 and NGF ($p<0.05$).
Conclusion: Serum Endocan and NGF levels increase with disease severity; Endocan and NGF can be used as target molecules in the psoriasis treatment.
Keywords: Psoriasis; Endocan; VEGF; CXCL12; NGF; Psoriasis Area and Severity Index

Introduction

Psoriasis is the most common chronic inflammatory immune-mediated skin sickness with hyperproliferation in the epidermis (1). Psoriasis affects people negatively physically, emotionally, and psycho-socially (2). The etiology of psoriasis, a disease affecting approximately 0.33-0.6% of the population, has not been fully elucidated. Its severity, characteristics, and prognosis differ between patients (3). In addition to the genetic predisposition, it plays an essential role in the emergence and recurrence of the disease in infections. Inflammation, atherosclerosis, and the development of vascular endothelial damage are effective in the etiopathogenesis of the disease, independent of conventional risk factors such as hypertension, age, diabetes, alcohol use, obesity, and smoking (2).

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Endocan is an organ-specific molecule expressed in vascular endothelial cells called endothelial-specific marker-1 (ESM-1) (4). It is also observed in serum where angiogenesis is predominant, especially in inflammatory diseases such as psoriasis and malignancy (4, 5).

ESM-1 gene expression, which plays a role in endothelium-dependent pathology, is regulated by cytokines. It has been shown that ESM1 expression increases in the being of pro-angiogenic growth factors such as nerve growth factor (NGF) (6), stromal cell-derived factor-1 (CXCL12) (7), and vascular endothelial growth factor (VEGF) (8), VEGF (9), CXCL12 (10), and NGF (6) levels are thought to be effective in the etiopathogenesis of psoriasis. These molecules are involved in inflammation and/or angiogenesis pathways. Since endocan is a molecule involved in angiogenesis and inflammation pathways, it can be thought that there may be a relationship between VEGF, CXCL12, and NGF.

The study aims to determine the endocan level in psoriasis and to reveal the correlation between endocan and VEGF, CXCL12, and NGF, which are reported to be involved in the pathogenesis of psoriasis. It is also to determine the relationship between these parameters and the severity of the disease.

Materials and Methods

Study Design

This study was conducted on 94 consecutive patients diagnosed with psoriasis in the Department of Dermatology of Harran University Medical Faculty Hospital (Jan 2020).

Ethical Statement

Permission for the present study was obtained from the Harran University Clinical Research Ethics Committee (Decision No: HRU.19.08.16). The authors declare that the patients included in the study signed informed consent forms to use their medical information in the studies.

Participant Selection

Inclusion criteria in the patient group; (i) be over 18 years old; (ii) to be diagnosed with psoriasis clinically and histopathologically; (iii) not having received systemic treatment for psoriasis in the last six months; (iv) not having received topical treatment for psoriasis in the last three months. The control group (n=100) was selected from patients who applied to the dermatology outpatient clinic and did not have any inflammatory disease (atherosclerotic heart disease, ulcerative colitis, psoriasis, Crohn's disease, connective tissue disease, etc.) for both groups; Diabetes, hypertension, dyslipidemia, cardiovascular disease, chronic liver disease, hypothyroidism diagnosis, those using anti-hyperlipidemic, anti-diabetic, antipsychotic drugs and those who did not approve the voluntary consent form were excluded from the study. In psoriasis and control groups, whole blood collected in a flat tube without anti-coagulant and gel was centrifuged at 4000 rpm for 10 minutes, then separated into tubes and stored at -80ºC.

Laboratory Analysis

Serum ESM-1 (Human Mouse ESM1 ELISA Kit), VEGF (Human Vascular Endothelial Growth Factor A (VEGFA) ELISA Kit), CXCL12 (Human Stromal Cell Derived Factor 1 (SDF1) ELISA Kit) and NGF (Human Nerve Growth Factor (NGF) ELISA Kit) levels were measured by ELISA method following the manufacturer's (MyBio Source, USA) instructions.

The Psoriasis Area and Severity Index (PASI) score was used to determine disease severity (11). According to PASI, patients were disunited into four groups as mild (n=11), moderate (n=46), severe (n=22), and very severe psoriasis patients (n=15).

Statistical Analysis

Data were analyzed with GraphPad Prism version 8 (USA). Shapiro Wilk, Mann Whitney, and Dunnett, multiple comparison tests, were used where appropriate. Results were accepted

as significant at p<0.05 at a 95% confidence interval. The correlation was analyzed with Spearman Correlation. Correlation coefficient performed as described by Koo et al. (12).

Results

A total of 194 subjects, including 94 psoriasis patients (50 females and 44 males) and 100 healthy controls (52 females and 48 males), were included in the study. There was no significant difference between the control group and the patient in the study regarding gender, age, and BMI (Table-1). Compared to the control group, serum endocan, VEGF, CXCL12, and NGF levels were found to be significantly higher in the psoriasis patient group (Table-1 and Figure-1). Psoriasis patients were grouped according to PASI. Compared to the control, endocan and NGF were higher in the mild and moderate groups. In the very severe psoriasis, VEGF was higher in the moderate and severe psoriasis group, and CXCL12 and FGF2 were higher in moderate, severe, and severe psoriasis groups (Table-2). In psoriasis, there was no correlation between endocan and VEGF (r=0.08; *p*=0.42). There was a moderate correlation between CXCL12 (r=0.58; *p*<0.0001) and NGF (r=0.60; *p*<0.0001) when compared with endocan (Figure-2).

Discussion

The present study showed for the first time that endocan, VGEF, CXCL12, and NGF levels were high in the serum of psoriasis patients, and the level of these parameters increased as the disease severity increased. Moreover, a

Table 1. Comparison of demographic and biochemical parameters in psoriasis patients and healthy control group

Variables		Psoriasis (n=94)	Control (n=100)	*P value*
Age (years)		37.82±14.82	36.1±12.87	0.566*
Gender	Female	50	52	x^2=0,02; p=0,86**
	Male	44	48	
BMI (kg/m^2)		22.47±4	22.1±2.71	0.623*
Endocan (ng/mL)		341.4±116,9	77.42±38,91	<0.0001*
VEGF (ng/mL)		287.4±98.68	235.7±77,82	0.0011*
CXCL12 (ng/mL)		1756±528.4	1254±568	<0.0001*
NGF (ng/mL)		149.3±49,99	52.61±51.13	<0.0001*

*Mann Whitney test; ** Chi-square.

Table 2. Comparison of biochemical and demographic variables in four different severity levels in psoriasis patients

Variables		*Psoriasis Severity*			
		Mild (n=11)	Moderate (n=46)	Severe (n=22)	Very Severe (n =15)
Age (years)		60.66±6.65	37.46±15.62	31.08±11.34	41.50±7.91
Gender	Female	6	25	13	9
	Male	5	21	9	6
BMI (kg/m^2)		24.89±3.75	21.7±4.43	22.74±3.33	24.03±3.08
Endocan (ng/mL)		160.8±38.13	301.9±49.75	394.8±17.91	529.3±81.36
VEGF (ng/mL)		238.8±104.6	286.6±88.8	325.4±99.46	269.3±108.7
CXCL12 (ng/mL)		1323±446.2	1596±391	1927±433	2306±573.4
NGF (ng/mL)		124.8±36.77	132.6±36.89	159±36.44	203.2±67.73

* P-values are given in Figure-2 with their comparisons.

positive correlation between serum endocan level and CXCL12 and NGF was revealed for the first time. The serum endocan level was higher in psoriasis patients than in the control group. There are limited studies investigating the endocan level in psoriasis patients.

The results of the studies have reported different results regarding the endocan level in psoriasis patients. Although Erek Toprak et al. (13) declared that the endocan level did not change in this harvesting group, this was very limited. Conversely, Sigurdardottir et al. (14)

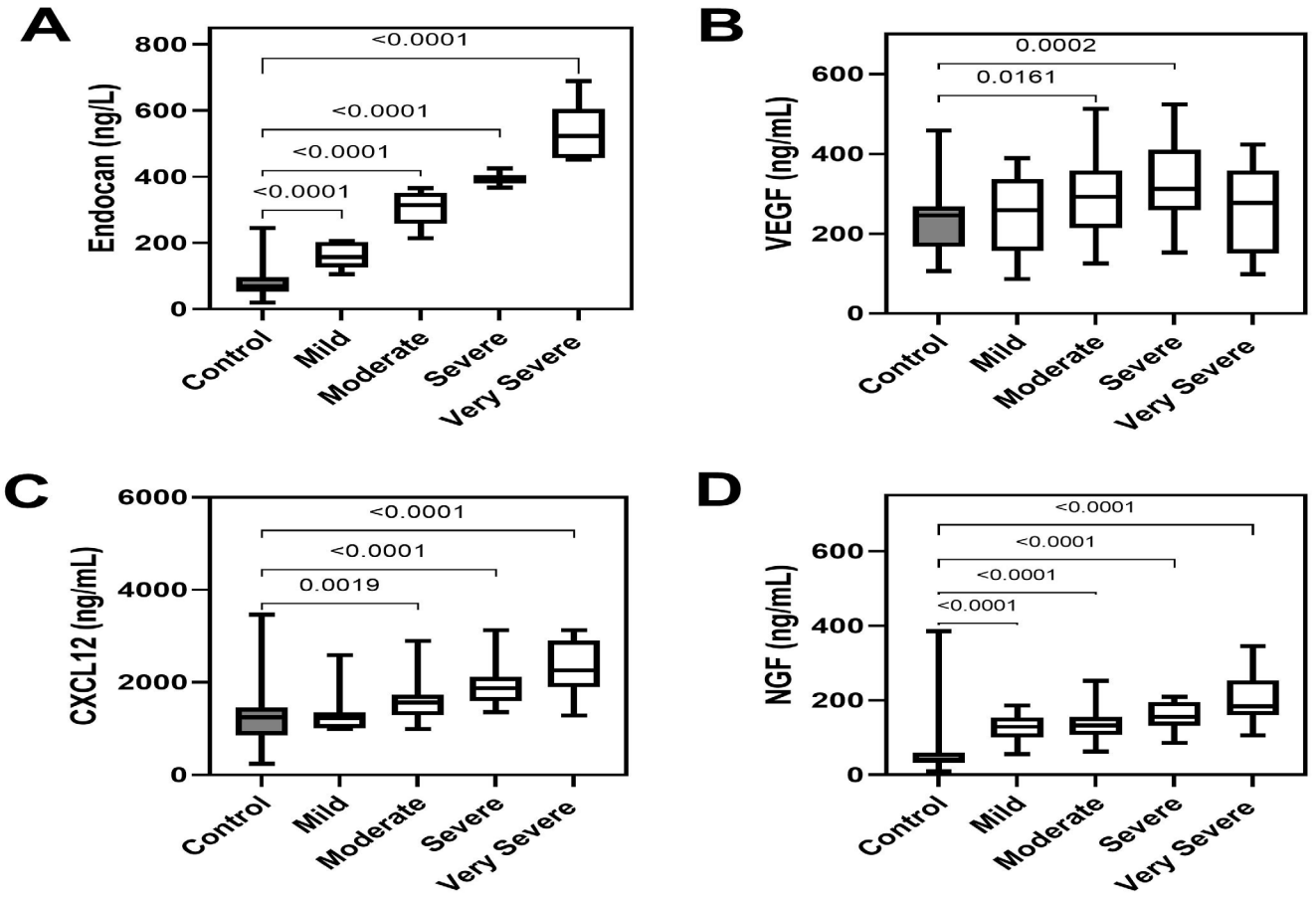


Figure 1. Comparison of serum endocan (A), VEGF (B), CXCL12 (C), and NGF (D) levels in psoriasis patients grouped according to disease severity

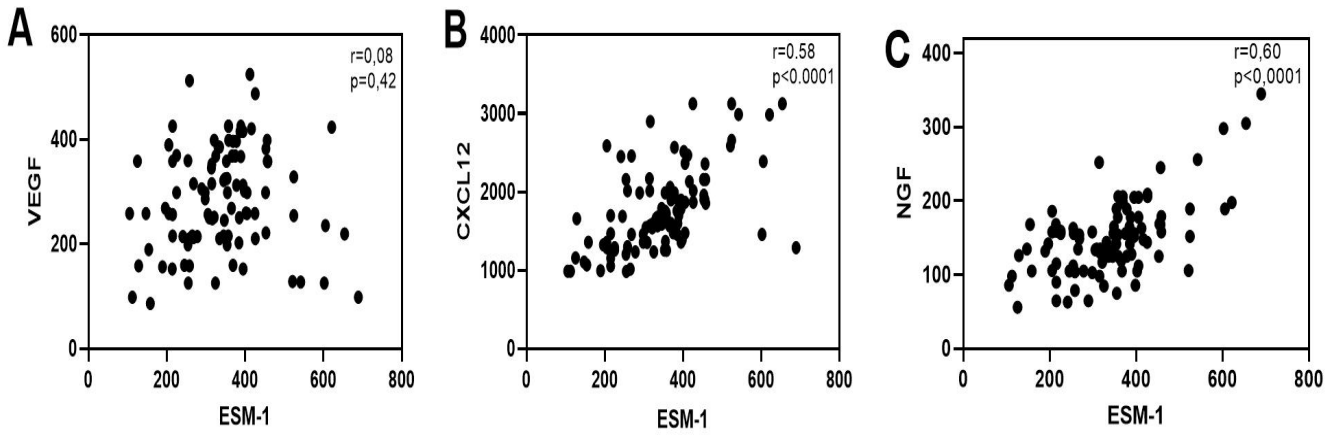


Figure 2. Correlation between serum endocan level and VEGF (A), CXCL12 (B), and NGF (C) level in psoriasis patients

reported that the endocan level was low in psoriasis patients compared to the healthy control. In the same study, UVB treatment increased the endocan level (14). In a study conducted with immunohistochemical staining of endocan by taking skin biopsies from 40 healthy subjects and 36 psoriatic patients (15), endocan was reported to be overexpressed from inflammatory cells, dermal endothelial and epidermal keratinocytes in psoriatic skin. In this study, endocan was suggested to enhance the proliferation and angiogenesis of psoriatic skin, which contributes to pathogenic mechanisms of psoriasis (15). Studies conducted with psoriasis vulgaris patients reported that the serum endocan was higher than that of healthy controls (16-19). The findings of this study also support these studies. In addition, when the endocan level of psoriasis disease severity (mild, moderate, severe, and very severe) was compared with healthy individuals, it was observed that as the disease severity increased, the endocan level increased.

In this study, the level of VEGF was high in psoriasis patients. In a study conducted on skin biopsies of psoriasis patients, high VEGF mRNA expression was reported (20). In another study, the serum level of VEGF was reported to be high in psoriasis patients (21). VEGF is a crucial growth factor regulating neovascularization during pathological processes, reproductive functions and embryogenesis (9). Angiogenesis is initiated by the activation of vascular endothelial cells by various agents. VEGF production and consequent excessive dermal vascularity are markers of psoriasis (9). VEGF, a critical angiogenic factor, is thought to play an essential role in the pathogenesis of psoriasis, and VEGF is suggested to be a promising target for the treatment of this disease (22). The findings obtained in this study support these results. In addition, VEGF was higher in moderate and severe psoriasis patients compared to healthy individuals according to the severity of psoriasis disease. There was no difference in other groups (mild and very severe psoriasis). It is thought to be important in revealing the relationship between disease severity and VEGF level in psoriasis patients for the first time. It is thought to be interesting to demonstrate that VEGF levels are not high in mild and severe patient groups. This was interpreted as neovascularization did not occur in the disease's mild to very severe stage. Considering the findings obtained in this study, the increase in VEGF level as the severity of the disease increases indicates that this molecule may be the target molecule that can be used to treat psoriasis. More comprehensive studies are needed on this subject.

As far as is known, no studies investigating serum CXCL12 levels in psoriasis patients have been reported. We think that our study is the first in this field. According to this study, serum CXCL12 level was higher in psoriasis patients than in healthy individuals. It was also shown for the first time that there is a relationship between disease severity and CXCL12 level. According to the PASI grouping, the CXCL12 level was higher in patients with moderate, severe, and severe psoriasis. Inflammation is essential in the pathogenesis of psoriasis. CXCL12 has a vital role in skin homeostasis and inflammation (10). High expression of CXCL12 mRNA was reported in a study conducted on skin biopsies of psoriasis patients (10). Considering the findings, it comes to mind that CXCL12 may play an active role in forming inflammation in the pathogenesis of psoriasis.

NFG level increases in psoriasis (23, 24). The findings obtained in this study support these studies. We also found that all groups' NGF levels increased as disease severity increased. This shows that NGF can be a candidate molecule for treating psoriasis. It has been shown that NGF protein levels are higher in psoriatic keratinocytes than in normal keratinocytes. Our findings support this study when evaluated in terms of serum (6).

In this study, there was no correlation between serum VEGF and endocan. This is the first time this condition has been reported in psoriasis patients. Psoriasis is an inflammatory disease. Similarly, inflammation is vital in pathogenesis of Behçet's disease. Kul et al. (25) reported a correlation between VEGF and endocan in Behçet's disease.

This study found a moderate positive correlation between serum endocan and NGF in psoriasis patients for the first time. Chen et al. (26) showed that ESM1 expression increased when NGFR+ murine OSCC cells were incubated with NGF. This finding supports our results. When the two studies are evaluated together, the increase in the NGF level may cause an increase in the endocan level.

This study showed a positive correlation between endocan and CXCL12 levels in psoriasis patients for the first time. CXCL12 has an essential role in skin homeostasis and inflammation (10). Similarly, endocan is a molecule involved in vascularization and inflammation. The existence of a correlation between these two molecules is thought to be compatible.

Conclusion

Consequently, endocan and NGF increased with disease severity. Considering these findings, endocan and NGF may be target molecules in the treatment of psoriasis. The positive correlation of serum endocan level with NGF supports this situation. The number of patients included in this study was based on a more significant number of patients than their peers. Since the center where the study was conducted is a region with a high population rate, the number of psoriasis patients is high. Therefore, the results are considered to be more reliable.

Conflict of Interest

The authors declare no conflict of interest for the present study.

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