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Neutrophil/Lymphocyte Ratio, Serum Endocan, and Nesfatin-1 Levels in Patients with Psoriasis Vulgaris Undergoing Phototherapy Treatment

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Background: Psoriasis is an autoimmune, inflammatory, and chronic disease. Recent studies have evaluated serum endocan and nesfatin-1 levels in patients with inflammatory disorders. The neutrophil-to-lymphocyte ratio (NLR) is an inflammatory marker currently used in many diseases. The aim of the present study was to evaluate NLR, serum endocan, and nesfatin-1 levels in psoriasis vulgaris before and after narrow-band ultraviolet B (NB-UVB) phototherapy treatment and compared to healthy controls.





Material/Methods: This study was conducted on a total of 88 cases, 39 of which had psoriasis vulgaris and 49 were healthy volunteers. Thirty-nine psoriasis vulgaris patients underwent NB-UVB phototherapy treatment for 3 months. NLR, serum endocan, and nesfatin-1 levels were measured in all psoriasis patients before and after NB-UVB phototherapy and in the control group.

Results: Compared with the control group, neutrophil count and NLR were significantly higher ($p < 0.001$) in psoriasis patients before NB-UVB phototherapy. Serum endocan levels were significantly correlated with disease activity before treatment. There was no significant difference in NLR, serum endocan, and nesfatin-1 levels in psoriasis patients before and after NB-UVB phototherapy ($p > 0.05$).

Conclusions: The current study shows that NLR was higher in psoriasis vulgaris patients when compared with the control group, whereas serum endocan and nesfatin-1 levels were not significantly different. In addition, NB-UVB phototherapy did not affect NLR, serum endocan, or nesfatin-1 levels. Further larger-scale studies are required on this subject.

MeSH Keywords: **Endocan • Nesfatin 1 • Neutrophil to Lymphocyte Ratio • Phototherapy • Psoriasis**

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Background

Psoriasis is an autoimmune, chronic, inflammatory skin disease affecting approximately 1–3% of the global population. Psoriatic skin lesions are characterized by sharp-edged, erythematous, squamous plaques and are histologically characterized by epidermal changes, inflammatory cell infiltration, and increased angiogenesis. The pathogenesis is multifactorial, and genetic, environmental, and immunological factors have been implicated in its pathogenesis [1].

Narrow-band UVB (NB-UVB) phototherapy is an important tool for treating psoriasis, but its mechanism of action has not been completely explained [2]. The clinical recovery in plaque-type psoriasis lesions after NB-UVB phototherapy is accompanied by a reduction in expression of interleukin 12 (IL-12), IL-18, and IL-23 [3]. IL-17 signaling pathways can be suppressed by effective NB-UVB phototherapy [4]. It has been shown that NB-UVB phototherapy suppressed the interferon (IFN) and T helper 17 (TH17) pathways in resolved psoriatic lesions [5].

Endocan is a recently described human endothelial cell-specific molecule. Endocan is expressed by the vascular endothelium and its release is controlled by various cytokines and growth factors [6]. Experimental studies show that endocan plays a major role in cell adhesion and tumor progression [7]. Endocan was identified as a potential endothelial cell marker [8]. A relationship has been suggested between tumor prognosis, metastasis, angiogenesis, and endocan expression [9]. Elevated serum endocan levels have been reported in dermatological disorders characterized by systemic inflammation, such as Behçet's disease and psoriasis. In addition, studies reported a correlation between disease activity and serum endocan levels [10,11].

Nesfatin-1 is a recently identified peptide. It is derived from the product of the NUCB2 (nucleobinding-2) gene [12]. Nesfatin-1 is released in the spinal cord, hindbrain, brainstem, forebrain, and adipose tissue [13]. Nesfatin-1 has anorexigenic effects and it has a major regulatory role in food intake, energy homeostasis, water intake, and body temperature [14,15]. In addition, nesfatin-1 has hypertensive effects [16].

Insulin plays important roles in skin physiology and homeostasis. There is a known relationship between insulin resistance and psoriasis. Psoriasis is associated with an increased risk of systemic diseases, such as diabetes mellitus, metabolic syndrome, and cardiovascular disease. Psoriasis is also more prevalent in obese patients. Chronic inflammation is the pathogenetic process underlying the close relationship between psoriasis and metabolic diseases [17]. A close relationship has been shown between nesfatin-1 and glucose, insulin metabolism, and insulin resistance [12,18]. To the best of our

knowledge, there is no study in the literature evaluating nesfatin-1 levels in patients with psoriasis.

The neutrophil-to-lymphocyte ratio (NLR) is a marker of systemic inflammation, currently used in many diseases. There are studies evaluating NLR in dermatological disorders such as psoriasis and Behçet's disease [19,20].

Although there are reports evaluating underlying factors in the pathogenesis of psoriasis disease, as far as we know there is no report evaluating NLR, serum endocan, and nesfatin-1 levels all together. Our study aimed to evaluate NLR, serum endocan, and nesfatin-1 levels in patients with psoriasis in comparison to a healthy control group. In addition, we also aimed to investigate the effect of NB-UVB phototherapy treatment on these parameters.

Material and Methods

Patient selection

The present study included 39 psoriasis vulgaris patients (mean age 34 ± 16 years) and 49 control subjects (mean age 38 ± 11 years). The study protocol was carried out in accordance with the Helsinki Declaration as revised in 2013. The study protocol was approved by the local ethics committee, and written informed consent was obtained from each subject. Inclusion criteria were age older than 18 years and moderate-to-severe plaque psoriasis for at least 6 months. Exclusion criteria were age younger than 18 years, pregnancy, lactation, infections, and a history of psoriasis treatment with systemic agents such as acitretin, methotrexate, cyclosporine, and biological agents within the last 4 weeks. Subjects with chronic diseases such as endocrine disorders, cardiovascular disease, hepatic disorders, hematologic disease, chronic renal failure, hypertension, or cancer were also excluded from the study.

Skin biopsy was performed in all psoriasis patients. Assessment of the disease severity was performed by using the Psoriasis Area and Severity Index (PASI) [21].

Phototherapy dose and technique

The whole-body irradiation was performed in a phototherapy cabinet (7001K cabinet, Waldman, Germany) containing 21 UVB lamps (Philips TL-01/100W) radiating light at the 311-nm wavelength. The initial UVB dosage before the treatment was determined according to the Fitzpatrick skin type (between 20 and 40 mJ/cm^2), and irradiation was performed 3 times a week and dosage increments were increased by 20% at each of the 2 sessions, depending on the erythema response.

Biochemical measurements

Blood samples were taken from patients in the morning after 12 h of fasting. Serum glucose, urea, creatinine, C reactive protein (CRP), total cholesterol, high-density lipoprotein (HDL), and triglyceride were analyzed by use of a Roche Cobas Integra 8000 (Germany) otoanalyzer with Roche Cobas reagent kits (Germany). Complete blood count was analyzed by using an Abbott Cell Dyn (Abbott Laboratories, IL, USA) analyser on the same day. The serum was obtained after centrifugation of the blood samples at 3500 rpm for 10 min and was kept frozen at -80°C in aliquoted microcentrifuge tubes for endocan and nesfatin 1 analysis.

Serum endocan and nesfatin-1 measurements

The human endocan and nesfatin-1 levels were analyzed by enzyme-linked immunosorbent assay (ELISA) using commercial kits (Aviscera Bioscience, USA and BioVendor Laboratories, Czech Republic, respectively), according to the manufacturers' instructions.

Intra-assay and inter-assay coefficient of variations (CV) of endocan assay were 6–8% and 10–12%, respectively. Sensitivity of the assay was 98 pg/ml. Upper limit of the standard was 25 ng/ml. Intra-assay CVs of nesfatin-1 assay were 2.75% and 5.75% for the concentrations of 6.7 and 0.83 ng/ml, respectively. Inter-assay CVs of nesfatin-1 assay were 5.43% and 6.29% for the concentrations of 3.81 and 6.89 ng/ml, respectively. Sensitivity of the assay was 0.021 ng/ml and the upper limit of the standard was 4 ng/ml.

Measurements were carried out using an ELISA plate reader (BioTek Instruments Inc, Winooski, VT, USA) and plate washer. Each well absorbance was determined at 450 nm. The standard curve was drawn by plotting the mean absorbance (Y) of standards against the known concentration (X) of standards in logarithmic scale, using the 4-parameter algorithm. Results are presented as ng/ml.

Statistical analysis

The statistical analyses were made using SPSS software version 16. Inc., Chicago, IL, USA). The distribution of continuous variables for normality was tested with a one-sample Kolmogorov-Smirnov test and data are presented as mean standard deviation (SD) or median and interquartile ranges, as appropriate. Categorical variables are reported as frequencies and group percentages. Differences between individuals with and without psoriasis vulgaris in normally and nonnormally distributed variables were evaluated by the unpaired t-test and the Mann-Whitney U test, respectively, as appropriate. The Wilcoxon signed ranks test was used to compare the

serum endocan and nesfatin-1 levels in patients with pre-and post-treatment status. The statistical set at evaluated at $p < 0.05$.

Results

Our study included 39 moderate-to-severe plaque-type psoriasis patients (17 males, 22 females) and 49 healthy controls (24 males, 25 females). The mean ages of psoriasis patients and controls were 34 ± 16 and 38 ± 11 years, respectively. The demographic, clinical characteristics, and biochemical measurements of this study are summarized in Table 1. There were no significant differences between the groups in terms of age or sex. PASI scores were 2.90–32.00 before treatment, with a mean value of 11.34 ± 7.29 .

The patients received 20–36 sessions of NB-UVB treatment. The total cumulative dose was between 26.85–76.85 joules/cm².

Fasting blood glucose ($p=0.43$), creatinine ($p=0.08$), high-density lipoprotein (HDL) ($p=0.06$), and triglyceride ($p=0.74$) levels were statistically similar between controls and psoriasis patients before NB-UVB phototherapy. White blood cell and neutrophil cell counts and NLR (Figure 1) were significantly higher in psoriasis patients before phototherapy ($p=0.001$, $p < 0.001$, and $p < 0.001$, respectively) when compared to controls. However, lymphocyte, hemoglobin, platelet, and mean platelet volume levels were similar between the 2 groups (Table 1) ($p > 0.05$).

There was no significant difference between psoriasis patients and controls in terms of serum levels of endocan before NB-UVB phototherapy ($p > 0.05$). In addition, no significant difference was detected between before-after NB-UVB phototherapy in psoriasis patients in serum levels of endocan ($p > 0.05$) (Table 2).

There was no significant difference between controls and psoriasis patients before phototherapy in serum levels of nesfatin-1 ($p > 0.05$). Of the patient group, the median serum nesfatin-1 levels increased after NB-UVB phototherapy, but was not significantly different from baseline ($p > 0.05$) (Table 3).

There was no significant difference in NLR before and after NB-UVB phototherapy in psoriasis patients ($p > 0.05$). The biochemical measurements of psoriasis patients before vs. after NB-UVB phototherapy are summarized in Table 1.

The correlation analyses in psoriasis patients showed that serum endocan levels were significantly correlated with pretreatment PASI score ($p: 0.006$, $r: 0.483$).

Table 1. Clinical, demographic characteristics and biochemical measurements of the participants.

		Control subjects (n=49)	Baseline psoriasis patients (n=39)	Post therapy psoriasis patients (n=39)	p (baseline difference)	P (Pre-post treatment)
Age, y		38±11	34±16		0.16	
Gender, M/F		24/25	17/22		0.61	
FBG, mg/dL	Median	93	92	88.00	0.43	0.72
	IR	86–98	81–97	79–96		
Urea, mg/dL		28.1±10.4	21.1±12.8	25.1±8.2	0.007	0.21
Creatinine, mg/dL	Median	0.77	0.69	0.77	0.08	0.23
	IR	0.64–0.91	0.61–0.83	0.69–0.84		
T.chol., mg/dL	Median	197	165	170	0.002	0.86
	IR	180–227	136–205	148–199		
HDL, mg/dL		54.1±15.3	48.1±10.4	49.5±10.9	0.06	0.96
TG, mg/dL	Median	91	95	94	0.74	0.40
	IR	66–161	64–154	70–157		
WBC, ×10 ³ /mm ³		6.5±1.8	8.1±2.1	7.7±1.9	0.001	0.14
Neutrophile, ×10 ³ /mm ³		3.74±1.39	5.16±1.75	4.96±1.96	<0.001	0.25
Lymphocyte, ×10 ³ /mm ³		2.19±0.63	2.21±0.62	2.10±0.61	0.96	0.19
Platelet, ×10 ³ /mm ³		246.6±66.4	256.6±76.3	253.8±86.9	0.53	0.86
MPV, fL		9.6±1.2	9.3±1.6	9.2±2.1	0.40	0.36
NLR	Median	1.66	2.39	2.22	<0.001	0.61
	IR	1.37–1.97	1.72–3.15	1.79–3.07		
Hgb, (g/L)	Median	14.10	13.00	13.40	0.09	0.02
	IR	12.8–15.2	12.1–14.6	12.5–14.9		
PASI			11.34±7.29			

Data are shown as mean ± standart deviation, median (25th–75th percentile) as appropriate. Comparison between groups was made by the student-t test or Mann-Whitney U and Chi-square test. P value less than 0.05 was considered to show a statistically significant result (p<0.05) *. Interquartile range: FBG – fasting blood glucose; TG – triglyceride; T.chol – total cholesterol; HDL chol – high density cholesterol; WBC – white blood cell; MPV – mean platelet volume; Hgb – hemoglobin; PASI – Psoriasis Area and Severity Index.

Discussion

The main findings of our study were that there was no significant difference in serum endocan and nesfatin-1 levels between psoriasis patients and controls, but there was a significant difference in NLR. Psoriasis patients had significantly higher NLR before NB-UVB phototherapy compared to the control group. It is remarkable that serum endocan levels were significantly correlated with disease activity before treatment. In addition, NB-UVB phototherapy did not affect NLR, serum endocan, or nesfatin-1 levels in psoriasis vulgaris patients.

Endocan is a 50-kDa dermatan sulfate proteoglycan [7]. Endocan is released by vascular endothelial cells, distal tubules of the kidneys, bronchi, and submucosal glands of the lungs [22]. Endocan expression is regulated by a series of growth factors and cytokines [7]. *In vitro* endocan expression is induced by tumor necrosis factor-alpha (TNF-α) and IL-1 beta, while IFN-gamma has been shown to inhibit endocan expression induced by TNF-α [23]. Endocan expression is strongly upregulated by vascular endothelial growth factor A (VEGF-A) and VEGF-C [24]. A study reported that serum endocan levels were elevated in psoriasis patients compared with control subjects

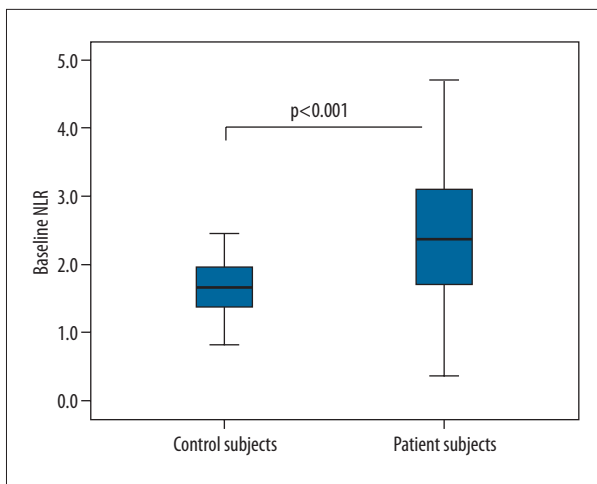


Figure 1. The NLR levels of psoriasis patients before NB-UVB phototherapy treatment and healthy control subjects.

and a positive correlation was demonstrated between endocan levels and disease activity, as well as cardiovascular risk [11]. Similarly, serum endocan levels are increased in Behçet’s disease patients compared to controls and endocan was reported to be a novel marker of disease activity [10]. Unlike these previous studies, the present study found no statistically significant difference in serum endocan levels between psoriasis patients and the control group.

Nesfatin-1 is a peptide released from the peripheral fat tissue, as well as from the central and peripheral nervous systems.

It suppresses food intake and stimulates insulin release from pancreatic cells; therefore, nesfatin-1 has been suggested to be a potential substance that could be used in the treatment of obesity and diabetes mellitus. Nesfatin-1 has different effects on many organs and organ systems of the human body, such as the immune system, cardiovascular system, nervous system, and endocrine system [25]. On the other hand, the effects of nesfatin-1 on dermatological diseases such as psoriasis have not yet been elucidated. There is no study in the literature that has evaluated nesfatin-1 levels in psoriasis patients. In the present study, there was no significant difference in serum nesfatin-1 levels between psoriasis patients and the control group, and we found that NB-UVB phototherapy did not affect serum nesfatin-1 levels.

In recent years, NLR has been regarded as a marker of inflammation in cardiac and non-cardiac disorders [26–28] and there have been many studies on NLR in inflammatory dermatological disorders. One study investigated NLR and platelet-to-lymphocyte ratio (PLR) in patients with psoriasis or psoriatic arthritis, reporting a positive correlation between NLR, PLR, and severity of disease in psoriasis patients. In addition, NLR and PLR were higher in psoriatic arthritis compared to psoriasis patients. NLR and PLR are strongly predictive of psoriatic arthritis in psoriasis patients [29]. Ataseven et al. [20] reported that NLR levels were higher in psoriasis patients as compared to a control group; however, there were no significant correlations between NLR and PASI. Sen et al. reported NLR and high-sensitivity CRP (hsCRP) levels were higher in psoriasis

Table 2. Serum endocan levels of psoriasis (before and after NB-UVB phototherapy treatment) and control groups.

	Psoriasis patients (n=39)	Control subjects (n=49)	P
Baseline endocan (ng/mL)	2.25 (1.83–3.15)	2.42 (1.89–2.88)	0.88
Endocan after phototherapy	2.29 (1.79–2.91)	–	–
p value	0.68	–	–

Data are presented as median (25th–75th percentile). Analysis between groups, Mann-Whitney U test; analysis of change within a group, Wilcoxon signed-rank test.

Table 3. Serum nesfatin-1 levels of psoriasis (before and after NB-UVB phototherapy treatment) and control groups.

	Psoriasis patients (n=39)	Control subjects (n=49)	P
Baseline nesfatin (ng/mL)	0.099 (0.058–0.185)	0.095 (0.033–0.203)	0.66
Nesfatin after phototherapy	0.105 (0.055–0.022)	–	–
p value	0.66	–	–

Data are presented as mean ± standart deviation. Analysis between groups, Mann-Whitney U test; analysis of change within a group, Wilcoxon signed-rank test.

patients than in a control group, and found a positive correlation between PASI levels and NLR and hsCRP levels [30]. In the present study, NLR levels were higher in psoriasis patients as compared to the control group, in agreement with previous reports. Also, NB-UVB phototherapy did not affect NLR in patients with psoriasis. In this regard, the present study is the first to investigate the effects of NB-UVB phototherapy on NLR.

This is the first study in the literature that evaluated nesfatin-1 levels in psoriasis patients, and it is also the first published study that evaluated the effects of NB-UVB phototherapy on NLR, serum endocan, and nesfatin-1 levels.

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Conclusions

The present study shows that NLR was higher in pretreatment psoriasis vulgaris patients when compared with controls, but serum endocan and nesfatin-1 levels were not significantly different. We found that serum endocan levels were significantly correlated with disease activity in pretreatment patients. In addition, NB-UVB phototherapy did not affect NLR, serum endocan, or nesfatin-1 levels. More comprehensive and larger-scale studies are needed to gain further insights into the role of endocan and nesfatin-1 in psoriasis pathogenesis and the effects of NB-UVB phototherapy on these molecules.

Declaration of interest

The authors report no conflicts of interest.