Original Investigation / *Özgün Araştırma*

Işıl Bulur, Hilal Kaya Erdoğan*, Evrim Çiftçi, Funda Canaz**, Semra Yiğitaslan***, Pınar Yıldız****, Zeynep Nurhan Saraçoğlu*, Muzaffer Bilgin*****

Evaluating the Role of Neurotrophins in the Psoriasis and Metabolic Syndrome Relationship

Psoriasis ve Metabolik Sendrom İlişkisinde Nörotrofinlerin Rolünün Değerlendirilmesi

Abstract

Objective: We aimed to evaluate the role of neurotrophins in relation to metabolic syndrome (MetS) and psoriasis by determining brain derived neurotrophic hormon (BDNF), nerve growth factor (NGF), tumor necrosis factor-α (TNF) and interleukin-6 (IL) levels in serum and skin samples of psoriasis patients and healthy controls.
Methods: The BDNF, NGF, TNF-α and IL-6 levels were assessed using commercially available ELISA kits. The level of expression BDNF, NGF, TNF-α and IL-6 antibodies was determined by BDNF, NGF, TNF-α and IL-6 Antibodies.
Results: Thirty nine psoriasis vulgaris patients without MetS risk factors, 21 patients with psoriasis vulgaris accompanied by MetS and 15 healthy controls were included in the study. The serum BDNF levels, epidermal and the dermal infiltration levels of BDNF were significantly higher in the control group than in the psoriasis patients (p=0.017, p=0.019, p=0.002). There was no difference between the groups in terms of serum NGF, TNF-α and IL-6 levels (p>0.05), but the infiltration level of NGF in the epidermis was higher in the psoriasis patients than the control group and statistically significant difference was found (p=0.003). Serum BDNF levels, epidermal and dermal BDNF infiltration level and the epidermal NGF staining intensity were similar among psoriasis patient groups (p>0.05).
Conclusion: The results of our study support the role of neurotrophins in the pathogenesis of psoriasis. However, serum and tissue BDNF and NGF levels remained unchanged among the psoriasis groups, suggesting that neurotrophins in the immunopathogenesis of psoriasis are related to the inflammatory process independently of the metabolic status.

Keywords: Brain derived neurotrophic hormon, nerve growth factor, neurotrophin, metabolic syndrome, psoriasis, immunopathogenesis

Öz

Amaç: Psoriasis hastalarında ve sağlıklı kontrollerde serum ve deri örneklerinde beyin türevli nörotrofik faktör (BDNF), sinir büyüme faktörü (NGF), tümör nekroz faktör-α (TNF) ve interlökin-6 (IL) düzeylerini belirleyerek metabolik sendrom (MetS) ve psoriasis ilişkisinde nörotrofinlerin yerini değerlendirmeyi amaçladık.
Yöntemler: Serum BDNF, NGF, TNF-α ve IL-6 düzeyleri ticari hazır ELISA kitleri ile değerlendirildi. BDNF, NGF, TNF-α ve IL-6 antikorları ile BDNF, NGF, TNF-α ve IL-6'nın derideki ekspresyon düzeyi belirlendi.
Bulgular: MetS risk faktörlerinden herhangi birinin eşlik etmediği 39 psoriasis vulgaris hastası, MetS'nin eşlik ettiği 21 psoriasis vulgaris hastası ile 15 sağlıklı kontrol çalışmaya dahil edildi. BDNF'nin serum, epidermal ve dermal infiltrasyon düzeyi kontrol grubunda psoriasis hastalarına göre belirgin olarak yüksek saptandı (p=0,017; p=0,019; p=0,002). Serum NGF, TNF-α ve IL-6 düzeyleri açısından gruplar arasında farklılık saptanmaz iken (p>0,05), psoriasis hastalarında epidermiste NGF'nin infiltrasyon düzeyi kontrol grubuna göre daha fazla olup istatistiksel olarak anlamlı fark tespit edildi (p=0,003). Psoriasis hasta grupları arasında ise serum BDNF düzeyi, epidermal ve dermal BDNF infiltrasyon düzeyi ve epidermal NGF infiltrasyon düzeyi ise benzerdi (p>0,05).
Sonuç: Çalışmamızdaki sonuçlar nörotrofinlerin psoriasis patogenezindeki yerini desteklemektedir. Ancak çalışmamızda psoriasis grupları arasında serum ve doku BDNF, NGF düzeylerinin değişmemiş olması, psoriasis immünopatogenezinde nörotrofinlerin metabolik durumdan bağımsız olarak inflamatuvar süreç ile ilişkili olduğunu düşündürmüştür.

Anahtar kelimeler: Beyin türevli nörotrofik faktör, sinir büyüme faktörü, nörotrofin, metabolik sendrom, psoriasis, immünopatogenez

Memorial Şişli Hospital, Clinic of Dermatology, İstanbul, Turkey

*Eskişehir Osmangazi University Faculty of Medicine, Department of Dermatology, Eskişehir, Turkey

**Eskişehir Osmangazi University Faculty of Medicine, Department of Patology, Eskişehir, Turkey

***Eskişehir Osmangazi University Faculty of Medicine, Department of Biochemistry, Eskişehir, Turkey

****Eskişehir Osmangazi University Faculty of Medicine, Department of Internal Medicine, Eskişehir, Turkey

*****Eskişehir Osmangazi University Faculty of Art and Science, Department of Statistics, Eskişehir, Turkey

Correspondence/ Yazışma Adresi:
Işıl Bulur, Memorial Şişli Hospital, Clinic of Dermatology, İstanbul, Turkey
Phone: +90 532 647 75 04
E-mail: isilbulur@yahoo.com
ORCID-ID: orcid.org/0000-0002-6041-3806
Submitted/Geliş Tarihi: 27.04.2017
Accepted/Kabul Tarihi: 13.07.2017

Introduction

The metabolic syndrome (MetS) is characterized by insulin resistance, obesity, glucose intolerance, hypertension and dyslipidemia. Genetic factors, diet, alcohol, drugs, psychosocial factors and neuroendocrine disorders as well as certain inflammatory diseases can trigger MetS development (1). The chronic inflammation in psoriasis patients is thought to be related to MetS, and relationship between the adipose tissue and psoriasis has been emphasized in the studies (2,3).

White adipose tissue is an endocrine organ and it secretes and synthesize various hormones. New studies have reported that the low-grade chronic inflammation is the source of obesity and triggers the disorders. Tumor necrosis factor-α (TNF), interleukin-1β (IL), IL-6, IL-8, IL-10, haptoglobulin, leptin and adiponectin are secreted from adipose tissue and initiate inflammation by passing into the circulation. The neurotrophins (NTs) are composed of nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), NT-3, NT-4 and NT-5 and are believed to be associated with inflammatory diseases as well as MetS (4,5). In recent studies, NTs have been reported to be effective not only on the peripheral and central nervous system but also on the immune and endocrine systems (6,7).

NGF is expressed in the nervous system and peripheral organs. The inflammatory process has been shown to start with NGF upregulation in many studies on inflammatory disorders. NGF increasing with IL-1, IL-6 and TNF-α stimulation plays an important role in the initiation of the chronic inflammatory process. The role of NGF and NGF-R have also been studied in psoriasis patients, and NGF was shown to increase inflammatory mediators, chemotaxis, cytokines and immunoglobulins in the studies (8).

BDNF is a recently identified NT, and responsible for the regulation of synaptic activities and development of neurons (6,9-12). Besides, it has been shown to be associated with lipid level elevation and to be a potential marker for the peripheral inflammatory response (6).

The objective of this study was to evaluate the serum and skin sample levels of BDNF, NGF, TNF-α and IL-6 in healthy controls and psoriasis patients, and investigate the relationship between MetS and psoriasis immunopathogenesis by determining the serum and skin sample levels of BDNF, NGF, TNF-α and IL-6.

Materials and Methods

Study population patients were clinically and histopathologically diagnosed with psoriasis vulgaris and healthy volunteers over the age of 18 were included in the study. The study protocol was approved by local ethics committee [The Ethics Commitee of Eskişehir Osmangazi University Faculty of Medicine (Number: 2014/2)]. The groups were divided into three groups as 39 psoriasis patients not accompanied with any MetS diagnosis criteria, 21 psoriasis patients with MetS, and 15 healthy volunteers.

Exclusion criteria were history of pregnancy, lactation, liver or kidney diseases, systemic inflammatory disease and systemic immunosuppressive treatment within the past one month. Besides, psoriasis patients other than psoriasis vulgaris were not included in the study.

Anthropometric measurements including height, weight, waist circumference and body mass index (BMI) measurements, and blood pressure values were recorded for psoriasis patients and controls. The disease severity was assessed by Psoriasis Area Severity Index (PASI) scoring.

National Cholesterol Education Program's ATP III was used for the MetS diagnosis (13). The presence of at least three of the followings is necessary for diagnosis of MetS: Waist circumference: ≥102 cm in men or ≥88 cm in women; triglycerides: ≥150 mg/dL; high-density lipoprotein cholesterol (HDL-C): <40 mg/dL for men, <50 mg/dL for women; blood pressure: ≥130 mmHg systolic or ≥85 mmHg diastolic; and fasting blood glucose (FBG): ≥110 mg/dL.

The Evaluation of Serum Samples

Venous blood samples taken from the patients after a fasting period of 12 h at 8 am were put in flat tubes and centrifuged at 3000 xg for 15 minutes. The routine parameters like fasting blood glucose, lipid profile; total cholesterol, triglycerides, HDL-C, low-density lipoprotein cholesterol (LDL-C) were evaluated. The remaining serum was stored at -80 °C until all samples were collected. BDNF (Human BDNF, Raybotech Elh-BDNF-001), NGF (Human NGF, Uscnk Sea105HU), TNF-α (Human TNF-α total Diasource Kap 1751) and IL-6 (Human IL-6, Diasource Kap 1261) levels in serum samples were identified quantitatively with the ELISA method. At the end of the ELISA study BDNF, NGF, TNF-α and IL-6 levels in each serum sample were calculated by performing regression-correlation analysis with Microsta, which is a computer-based statistics program, using the OD (optic density) of calibrators with known concentration. Plaques were evaluated spectrophotometrically at 450 nm with an automatic ELISA reader.

The Evaluation of Skin Biopsy Samples

A 4 mm skin biopsy was taken with the punch technique from the psoriatic lesions in areas of the body that was not exposed to sunshine from the patients and the gluteal region of the healthy volunteers. Histopathological evaluation was performed by the pathologists. BDNF (sc-546, rabbit polyclonal, IgG, Santa Cruz®), NGF (ab52918, Abcam), TNF-α (sc-52746, mouse monoclonal, IgG1, Santa Cruz®) and IL-6 (sc-130326, mouse monoclonal, IgG2b, Santa Cruz®) antibodies were used to determine BDNF, NGF, TNF-α and IL-6 expression in skin biopsies.

Cytoplasmic and nuclear staining in keratinocytes in the epidermis and lymphocytes in the dermis for BNDF, and cytoplasmic staining in keratinocytes in the epidermis and lymphocytes in the dermis for NGF, TNF-α and IL-6 were accepted as positive. Skin samples were classified as follows by the expression intensity of BDNF, NGF, TNF-α and IL-6: negative cases were scored as "0", low staining intensity were identified as 1+, moderate staining intensity as 2+, high staining intensity as 3+.

Statistical Analysis

Continuous values were presented as mean ± standard deviation. Categorical data were presented as percentages (%). The Shapiro-Wilk test was used to evaluate compliance of the data to the normal distribution. Independent sample t

test analysis was used for two groups and One-way variance analysis (One-Way ANOVA) for three or more groups in the comparison of the groups with a normal distribution. The Mann-Whitney U test was used for two groups and the Kruskal-Wallis H test for three or more groups in the comparison of the groups not conforming to a normal distribution. Pearson correlation coefficients were calculated for variables with a normal distribution and Spearman correlation coefficients for variables without a normal distribution for the determination of the direction and size of the relationship (correlation) between the variables. The IBM SPSS Statistics 21.0 program was used for the analyses. A p value <0.05 was accepted as statistical significance.

Results

This study included 39 psoriasis vulgaris patients without MetS, 21 psoriasis vulgaris patients with MetS and 15 healthy volunteers. These three groups were similar in terms of sex. BMI measurement and serum FBG, triglyceride, total cholesterol and LDL-C levels were statistically significantly higher in psoriasis patients than the in control group, and also in psoriasis patients with MetS than in psoriasis patients without MetS. While no statistically significant difference was present between the three groups in terms of the serum HDL-C levels, the serum HDL-C in psoriasis patients without MetS was statistically significantly higher than in the psoriasis patients with MetS. There was no statistically significant difference between the psoriasis patients with or without MetS in terms of the PASI value. Table 1 shows the demographic characteristics and laboratory values.

The mean serum BDNF, NGF, TNF-α and IL-6 levels of psoriasis patients and healthy volunteers are presented in Table 2. The values of the serum BDNF, NGF, TNF-α and IL-6 levels were statistically corrected for age. There was no statistically significant difference in terms of the serum NGF, TNF-α and IL-6 levels, but serum BDNF levels was significantly higher in the control group than the psoriasis patients (p=0.501, p=0.545, p=0.875, p=0.017, respectively, Table 2). Evaluation between the psoriasis patients with and without MetS groups revealed no statistically significant difference in terms of serum BDNF, NGF, TNF-α and IL-6 levels (p=0.522, p=0.064, p=0.428, p=0.868, respectively, Table 2).

The staining intensity of BDNF in epidermis and dermis were higher in the control group and a statistically significant difference was present between the groups (p=0.019, p=0.002). The the staining intensity of BDNF in the epidermis and dermis were similar in two psoriasis patient groups (p=0.478, p=0.540). Figure 1a shows the BDNF staining of the epidermis and dermis in a psoriatic lesion.

The staining intensity of NGF in the epidermis was higher in psoriasis patients than in the control group, and a statistically significant difference was found (p=0.003). When psoriasis patients were compared in two groups as those with and without MetS, the staining intensity of NGF in the epidermis was found to be similar (p=0.807). When these three groups and then the psoriasis patients were compared between each other no statistically significant difference was found in terms of NGF staining intensity in the dermis (p=0.204, p=0.807). The staining of the epidermis and dermis with NGF in a psoriasis lesion is shown in Figure 1b.

There was no statistically significant difference in three groups and between psoriasis patients in terms of staining

Table 1. Demographic characteristics and laboratory values of the patient and control groups

	Psoriasis with MetS (n=39)	Without MetS (n=21)	Control (n=15)	p
Age	39.00±13.59	46.95±10.68	36.73±10.07	0.020* (0.024¥)
Gender **Female** **Male**	 16 (41.0%) 23 (59.0%)	 10 (47.6%) 11 (52.4%)	 8 (53.3%) 7 (46.7%)	0.465
BMI (kg/m²)	26.35±4.92	33.55±5.16	25.56±2.92	<0.0001* (<0.0001¥)
PASI	12.29±5.39	13.58±7.28	-	(0.750¥)
FBG (mg/dL)	87.00±17.52	140.09±70.75	86.93±8.41	<0.0001* (<0.0001¥)
Triglyceride (mg/dL)	105.82±51.72	173.95±41.12	112.83±32.28	<0.0001* (<0.0001¥)
Total cholesterol (mg/dL)	176.38±41.88	207.95±39.38	191.67±36.06	0.017** (0.006§)
LDL-C (mg/dL)	115.33±36.85	149.48±38.06	136.33±31.12	0.003** (0.001§)
HDL-C (mg/dL)	48.97±12.97	43.52±11.05	45.60±14.46	0.133* (0.044¥)

*The Kruskal-Wallis Test and **One-Way ANOVA test were used in the comparison between the three groups

¥The Mann-Whitney U test and the Independent Samples test were used in the comparison between psoriasis patients with and without MetS. The p values are presented in parentheses

p values <0.05 were accepted as statistically significant

MetS: Metabolic syndrome, BMI: Body mass index, PASI: Psoriasis Area and Severity Index, FBG: Fasting blood glucose, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density cholesterol

intensity of TNF-α and IL-6 in the epidermis and dermis (Table 3, Figure 1c, 1d).

While no correlation was found between serum NGF and BDNF levels and serum TNF-α, IL-6 and metabolic parameters; moderate positive relationship was found between BDNF and NGF levels in psoriasis patients with and without MetS (Table 4).

Discussion

Recent studies have suggested that chronic inflammation plays an important role in the development of MetS and obesity, and neurotrophins are thought to be one of the factors in the pathogenesis of this inflammation (6). BDNF and NGF were reported to be associated with diabetes and cardiometabolic risk factors in addition to their neurological effects (7,12,14-17). Chaldakov et al. (3,18) emphazised that the decrease in NT levels is related to obesity and cardiovascular risks, and the hyponeurotrophinemia is seen in MetS and cardiovascular diseases. Besides, a decrease in serum BDNF levels secondary to inflammation was shown in several studies (19,20).

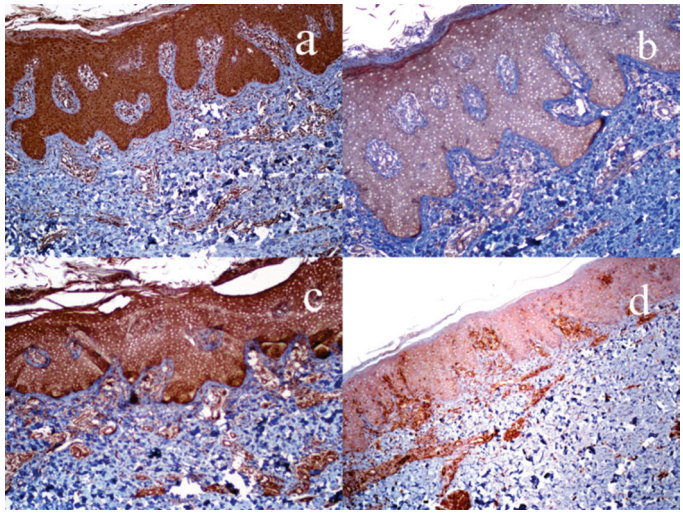

Figure 1. a) Immunohistochemically there was 3+ staining with brain derived neurotrophic hormon in the epidermal keratinocytes and 3+ staining in the dermal lymphocytes, b) Immunohistochemically there was 3+ staining with nerve growth factor in the epidermal keratinocytes and 3+ staining in the dermal lymphocytes, c) Immunohistochemically there was 2+ staining with tumor necrosis factor -α in the epidermal keratinocytes and 3+ staining in the dermal lymphocytes, d) Immunohistochemically 1+ staining with interleukin-6 in keratinocytes in the epidermis and 3+ staining in lymphocytes in the dermis

There are only a few studies about the serum BDNF, NGF levels and psoriasis relationship in the literature. Brunoni et al. (21) observed low levels of plasma BDNF in psoriasis patients, and they suggested that this result supported the brain-skin connection in psoriasis pathogenesis. Raap et al. (22) included psoriasis patients and healthy volunteers as a control group in the study where they evaluated serum BDNF and NGF levels in intrinsic atopic dermatitis. They reported lower serum BDNF and NGF levels in psoriasis patients than in atopic dermatitis, and the BDNF levels in psoriasis patients were also lower than in the healthy group. Conversely, Schulte-Herbrüggen et al. (23) stated that the serum NGF levels in psoriasis and atopic dermatitis patients showed a significant increase compared to healthy controls. However, there is only one study evaluating the relationship between NT levels and metabolic condition in psoriasis patients. In their study, Quan et al. (24) mentioned that the psoriasis risk and disease severity increase with a high BMI value and the BDNF rs6265 (GG) polymorphism. Although we detected the low serum BDNF levels in psoriasis patients, no difference was found between the psoriasis patients with and without MetS. Therefore, we think that the low BDNF levels was secondary to the inflammation in psoriasis rather than the metabolic condition. On the other hand, serum NGF levels was not different between the psoriasis patients with and without MetS, and between the healthy controls and psoriasis patients in our study.

Human basal keratinocytes secrete biologically active BDNF and NGF (25). BDNF shows its effect by triggering keratinocyte apoptosis via p75NTR (26). Truzzi et al. (26) observed that the apoptosis triggered by the BDNF and p75NTR interaction was significant in keratinocytes in the normal skin but not in psoriatic skin. In our study, the low BDNF infiltration levels in epidermis and dermis in psoriasis patients support these

Table 2. The comparison of serum brain derived neurotrophic hormon, nerve growth factor, tumor necrosis factor-α and interleukin-6 levels between groups

	Psoriasis with MetS (n=39)	Without MetS (n=21)	Control (n=15)	p
BDNF (ng/mL)	3.15±2.44	3.00±2.99	5.39±3.65	0.017* (0.522¥)
NGF (pg/mL)	218.64±103.41	186.81±92.49	227.59±262.13	0.501* (0.064¥)
TNF-α (ng/mL)	212.13±86.31	194.13±56.87	187.48±90.19	0.545* (0.428¥)
IL-6 (ng/mL)	417.65±117.45	423.79±102.78	397.01±02	0.875** (0.868$)

*The Kruskal-Wallis test and **One-way ANOVA test were used in the comparison between the three groups
¥The Independent Samples T test and the $Mann-Whitney U test were used in the comparison between the psoriasis patients with and without MetS and the p values were presented in parentheses
p values <0.05 were accepted as statistically significant. Values were statistically corrected for age
MetS: Metabolic syndrome, BDNF: Brain derived neurotrophic hormon, NGF: Nerve growth factor, TNF-α: Tumor necrosis factor-α, IL: Interleukin

Table 3. Comparison of brain derived neurotrophic hormon, nerve growth factor, tumor necrosis factor-α and interleukin-6 infiltration levels in skin samples between groups

	Psoriasis With MetS (n=39)	Without Mets (n=21)	Control (n=15)	p
BDNF epidermis	2 (2-3)	2 (2-3)	3 (3-3)	0.019* (0.478$)
BDNF dermis	3 (2-3)	2 (2-3)	3 (3-3)	0.002* (0.540$)
NGF epidermis	1 (1-2)	2 (1-2)	1 (0-1)	0.003* (0.807$)
NGF dermis	1 (1-2)	1 (1-2)	2 (1-2)	0.204* (0.807$)
TNF-α epidermis	1 (1-2)	2 (1-2)	2 (1-3)	0.225* (0.695$)
TNF-α dermis	2 (2-2)	2 (2-3)	2(2-3)	0.076* (0.129$)
IL-6 epidermis	0 (0-1)	1 (0-1)	1 (0-2)	0.188* (0.583**)
IL-6 dermis	3 (2-3)	3 (3-3)	3 (3-3)	0.54* (0.066$)

*The Kruskal-Wallis test and **One-way ANOVA test used for the comparison between the three groups
$The Mann-Whitney U test was used for the comparison between psoriasis patients with and without metabolic syndrome$ and the p values were given in parentheses
p values <0.05 were accepted as statistically significant
MetS: Metabolic syndrome, BDNF: Brain derived neurotrophic hormon, NGF: Nerve growth factor, TNF-α: Tumor necrosis factor-α, IL: Interleukin

Table 4. Correlation between serum brain derived neurotrophic hormon and nerve growth factor levels and study parameters

	Serum BDNF				Serum NGF			
	MetS (-)		MetS (+)		MetS (-)		MetS (+)	
	r	p	r	p	r	p	r	p
PASI	-0.173	0.293	-0.236	0.302	-0.114	0.491	-0.138	0.552
Serum BDNF (ng/mL)	0.547	<0.001	0.226	0.324	-	-	-	-
Serum NGF (pg/mL)	-	-	-	-	0.547	<0.001	0.226	0.324
Serum TNF-α (ng/mL)	0.280	0.085	0.047	0.838	0.304	0.060	0.162	0.482
Serum IL-6 (ng/mL)	0.220	0.179	-0.006	0.980	0.120	0.467	-0.120	0.606
BDNF epidermis	0.266	0.102	-0.135	0.559	0.010	0.954	-0.255	0.265
BDNF dermis	0.198	0.226	-0.244	0.286	0.020	0.903	-0.266	0.245
NGF epidermis	-0.016	0.921	-0.340	0.131	-0.248	0.128	0.080	0.732
NGF dermis	0.007	0.965	0.090	0.699	-0.026	0.877	0.106	0.648

MetS: Metabolic syndrome, BDNF: Brain derived neurotrophic hormon, NGF: Nerve growth factor, TNF-α: Tumor necrosis factor-α, IL: Interleukin, PASI: Psoriasis area and severity index

findings. On the other hand, the infiltration intensity of BDNF in the lesion being similar in patients with and without MetS indicates that this difference is caused by current inflammation, independent from the metabolic situation.

Autocrine NGF protects the cells from programmed cell death (26). The NGF levels were higher in the epidermis in psoriatic skin than in healthy skin and psoriatic skin without lesions (26). Raychaudhuri et al. (27) showed that keratinocytes express higher NGF and NGF-R in psoriatic skin than in healthy controls. Cutaneous trauma, keratinocyte proliferation and NGF upregulation in basal keratinocytes were reported to be the main factors stimulating T lymphocyte epidermotropism in their study. Besides, Baerveldt et al. (28) evaluated serum NGF, GATA3, IL-22RA1 levels and antimicrobial peptides during ustekinumab treatment. They mentioned that NGF showed a significant increase in psoriatic lesions while a decrease was observed after treatment (28). In our study, consistent with the literature results, the NGF infiltration levels in the epidermis in psoriasis patients were found to be statistically significantly higher than in the control group, but no difference was seen between the psoriasis patients with and without MetS. This result showed that the increased NGF infiltration intensity in epidermis could not affect the serum NGF levels in psoriasis patients.

The increase in TNF-α and IL-6 serum levels in MetS also play a role in the pathogenesis in psoriasis patients (2-7,29). TNF-α and IL-6 serum and tissue levels were similar in all three groups in our study. We did not observe any relationship between

the serum BDNF, NGF levels and the TNF-α, IL-6 levels and metabolic parameters in psoriasis patients. This result may indicate that TNF-α and IL-6 does not always play a role as a major cytokine in the pathogenesis of MetS in psoriasis. Besides, these results demonstrate the heterogeneity of the patient-based inflammatory cytokine network in psoriasis.

No statistically significant correlation was seen between serum BDNF and NGF levels and serum TNF-α, IL-6 levels and metabolic parameters. We also did not detect the relationship between the levels of BDNF and NGF in the serum and skin samples and the PASI value in patient groups. Consistent with our results, Schulte-Herbrüggen et al. (23) found no relationship between the serum NGF level and PASI values in psoriasis patients and Brunoni et al. (21) found plasma BDNF levels to be similar in moderate and severe psoriasis cases.

Study Limitations

The study limitation is the small number of the patients included in the study.

Conclusions

In conclusion, the serum BDNF levels and the staining intensity of BDNF in epidermis and dermis of the psoriasis patients were significantly lower than in the control group, independent of MetS; while NGF infiltration in the epidermis was found to be significantly increased in this study. Although the evaluation of the difference between BDNF and NGF levels in patients accompanied by MetS or not was the primary aim of our study, these results led us to think neutrophins may be related to the inflammatory process independent from the metabolic situation in psoriasis pathogenesis. Besides, we believe that these results may have an effect on the detection of target molecules for the treatment of psoriasis.

Ethics

Ethics Committee Approval: The Ethics Commitee of Eskişehir Osmangazi University Faculty of Medicine (Number: 2014/2).

Informed Consent: Informed consent was signed by the volunteers.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: I.B., P.Y., Z.N.S., Design: I.B., Data Collection or Processing: I.B., H.K.E., Analysis or Interpretation: E.Ç., F.C., S.Y, M.B., Literature Search: I.B., H.K.E., P.Y., Z.N.S., Writing: I.B.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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