



## Serum Cytokine Profiles in Patients with Psoriasis

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### Abstract

Psoriasis is a common inflammatory autoimmune skin disease that affects 2 - 4% of the world's population. T cells including adipocytokines such as chemerin, Transforming Growth Factor- $\beta$ 1 (TGF $\beta$ 1), FMS-associated Tyrosine kinase 3 ligand (FLT3-Ligand), Tumor Necrosis Factor Alpha (TNF $\alpha$ ) and Interleukin  $\beta$  1 (IL-  $\beta$  1) infiltration, interleukins and cytokines play a role in the pathogenesis of psoriasis.

In this study, we aimed to evaluate the pathogenesis of psoriasis disease and to evaluate serum chemerin, serum lipid profiles, body mass index, and Psoriasis Area Severity Index (PASI) values in psoriasis patients who applied to dermatology polyclinic.

Serum chemerin, TGF  $\beta$ 1, FLT3-Ligand, TNF  $\alpha$ , and IL- $\beta$  1 levels were investigated using the Enzyme-linked immunosorbent assay (ELISA) method. Serum C-reactive protein, total cholesterol, LDL, triglyceride fasting glucose and white blood cell levels were also evaluated. A total of 80 individuals (37 psoriasis and 43 healthy controls) were admitted to Gaziantep University Medical Faculty Dermatology Polyclinic between July 2016 to April 2017. Assessment of the activity of psoriasis was made with the PASI score.

According to the results of this study, serum levels of chemerin, TGF $\beta$ 1, FLT3-Ligand, IL- $\beta$ 1 and TNF $\alpha$  were found to be higher in patients with psoriasis than those in the control group ( $p < 0.01$ ,  $p < 0.05$ ,  $p < 0.01$ ,  $p < 0.01$ , and  $p < 0.01$ ). There was a significant positive correlation between PASI score and serum chemerin level ( $r = 0.695$  \*\*  $p < 0.01$ ). Serum total cholesterol, LDL and triglyceride levels of the control group were found to be lower as compared to the patient group and it is statistically significant ( $p < 0.01$ ,  $p < 0.01$  and  $p < 0.05$ , respectively). Serum total cholesterol, LDL and triglyceride levels of the control group were also found to be lower than those for the patient group and it is statistically significant ( $p < 0.01$ ,  $p < 0.01$  and  $p < 0.05$ , respectively). White blood cell counts (WBC) were significantly higher in the patient group ( $9.03 \pm 3.31$  versus  $6.71 \pm 1.65$ ) ( $p < 0.01$ ). CRP, PASI score were found to be positively correlated with serum chemerin level and the relations are statistically significant ( $r = 0.425$  \*\*  $p < 0.01$ ) ( $r = .515$  \*\*  $p < 0.01$ ).

As a result, high serum levels in patients with psoriasis indicate an inflammatory process and markers such as TGF  $\beta$ 1, FLT3-Ligand, IL- $\beta$  1 and TNF  $\alpha$  may be useful in determining the severity of psoriasis.

**Keywords:** Psoriasis; Chemerin; TGF  $\beta$ 1; FLT3-Ligand; IL- $\beta$  1; TNF  $\alpha$

## Introduction

Psoriasis is a chronic, incurable, hereditary, debilitating disease, and autoimmune inflammatory dermatosis that affects 2 - 3% of the population. The development of psoriasis had shown to be affected by immunological, genetic and environmental factors, but the main reasons behind psoriasis still not fully understood. Although the causes of psoriasis are not clear but numerous danger factors are known, involved family history and environmental risk agents, like smoking, overwork, obesity, and alcohol consumption [1].

This skin is characterized by red, crusty plaques, that can coats all parts of the human body has a great psychological and physical effects on the persons daily life even more than many other chronic medical diseases like diabetes or cancer [2]. Many inflammatory molecules as cytokines and chemokines or growth factors were shown as included in psoriasis pathogenesis. However, it was known that several immune cells such as T-helper1 (Th-1) and T-helper17 (Th-17) were had a role in the development of psoriasis. Local T-cells and macrophages in the psoriatic lesion lead to releasing of many kinds of cytokine and chemokine. Anti-psoriatic therapies were used to prevent T-cells and interleukins from achieving partial or total psoriatic effects [3]. Psoriasis is associated with systemic disorders as well as being a skin disease. Various observational studies have shown associations between psoriasis and serious comorbidities such as obesity, that obesity may contribute to psoriasis susceptibility and severity. Psoriasis is not a fatal disease but affects the life quality and family life of patients. Significant amounts of evidence suggest that adipose tissue is an active endocrine organ that secretes a variety of bioactive proteins or adipocytokines. such as chemerin, contributing to the regulation of body functions such as immune-mediated processes and inflammation [4,5]. Also, macrophage and dendritic cell activation and chemotaxis can be modulated by chemerin [6].

Obesity contributes to the pathogenesis of psoriasis by stimulating excessive production of multiple pro-inflammatory cytokines as tumor necrosis factor (TNF-a), IL-6, IL-8 and reactive C protein (CRP) in adipose tissue. However, the high body mass index correlates with the severity of psoriasis [7].

Transforming Growth Factor  $\beta$  1 (TGF $\beta$  1) is defined as a cytokine with its three isoforms in human tissues and contributes the cell growth and differentiation. TGF $\beta$ 1 is the dominant isoform in the majority of tissues, including the skin. Serum TGF $\beta$ 1 levels are elevated in psoriasis patients and found significantly lower after treatment. Increased amounts of TGF $\beta$ 1 in psoriatic patients are thought to originate from fibroblasts, activated endothelial cells or inflammatory cells [8].

The FMS-associated Tyrosine kinase 3 ligand (FLT3-Ligand) is an important cytokine involved in the hematopoiesis process. The receptor of FLT3-Ligand leads to growth and differentiation of myeloid, dendritic and lymphoid cells. The FLT3-Ligand is needed for the formation of dendritic cells, which are important in the immunopathology of psoriasis [9].

Interleukin-1 $\beta$  (IL-  $\beta$ 1) is an inflammatory cytokine, produced by dendritic cells, monocytes, macrophages and keratinocytes. It supports the functioning of some type T cells and leads to the secretion of IL-17 and IL-22. IL-1 $\beta$  is a potent inflammatory agent in the pathogenesis of psoriasis and activates keratinocytes that produce keratin 6 and keratin 16 [10].

Tumor Necrosis Factor Alpha (TNF $\alpha$ ) is a pro-inflammatory cytokine that has a basic role in the pathogenesis of psoriasis. Irregular TNF $\alpha$  production and TNF receptor coding have been connected with the development of this disease [7].

Dendritic cell types with a major contribution to the pathogenesis of psoriasis are myeloid dendritic cells and plasmacytoid dendritic cells present antigens and produce pathogenic agents such as TNF $\alpha$ . Dendritic cells provide antigen presentation and identify the immune response due to through the cytokines secreted in psoriasis to determine the exact polarity of the T cell to which the immune response will come or not. Myeloid dendritic cells, highly specific DCs in the psoriasis formation, produce TNF- $\alpha$  and provide Th1 and Th17 polarity of naive T cells. TNF- $\alpha$  is also generated by T cells, keratinocytes and various cell types and nowadays, psoriasis can be successfully treated by blocking TNF-  $\alpha$ . This interaction plays an important role in the pathogenesis of autoimmune diseases, leading to the secretion of cytokines, including TGF- $\beta$ 1, FLT3 ligand, IL- 1 $\beta$  and TNF- $\alpha$  [11,12].

## Purpose of the Study

The purpose of this study is to evaluate the roles of an adipocytokine chemerin and cytokines as TGF- $\beta$ 1, FLT3-Ligand, IL- 1 $\beta$  and TNF $\alpha$  in the pathogenesis of psoriasis. It is also aimed to investigate the metabolic and inflammatory profiles of patients with psoriasis together with BMI and Psoriasis Area Severity Index (PASI).

## Material and Methods

### Patient selection

Patients followed with psoriasis vulgaris that diagnosed histopathologically, between the years 2016 - 2017 at the Gaziantep University School of Medicine, Department of Dermatology, age and sex-matched healthy volunteer subjects were included in the study. Patient files were screened and information such as sociode-

mographic characteristics, known diseases, history of family, drugs used, and routine laboratory tests were obtained retrospectively.

Approval was obtained for this research with the decision of the local Ethics Committee dated 31.10.2016 and 2016/279 and the study was conducted in compliance with the Helsinki Declaration Rules. All patients participating in the study were informed about the study and their written consent was obtained.

Patients who were using cytotoxic, antihyperlipidemic, anti-biotic, antioxidant drugs, cigarettes, alcoholic beverages, having chronic disease, acute or chronic infection excluded. Psoriasis Area and Severity Index (PASI) was used to evaluate the severity of the disease.

### Blood sample collection and preparation

Venous blood samples were collected from each patient and control individuals after 12 hours fasting and centrifuged for 8-10 minutes until 4000 rpm after coagulation the resulting sera were aliquoted into micro tubes and either immediately frozen at -80°C. These samples were placed in the refrigerator at 4°C temperature one night before the measurements. The serum samples were allowed to rest at room temperature for 2 hours before working with the ELISA method. Later, measurement procedures were implemented by mixing the samples using a vortex. All measurements were performed twice and concentration/absorption graphic curves of research parameters such as chemerin, Transforming Growth Factor-β1 (TGFβ1), FMS-associated Tyrosine kinase 3 ligand (FLT3-Ligand), Tumor Necrosis Factor Alpha (TNFα) and Interleukin β 1 (IL-β 1) and calculations on the results were conducted on a program of the device Biotek\_ELx808 (Winooski, Vermont, ABD).

### Chemerin measurement

Serum chemerin levels were assessed with a commercially available quantitative sandwich-enzyme-linked immunosorbent assay (ELISA) kit, following the manufacturer's instructions (Rel Assay Diagnostics® Mega Tip Ltd, Turkey). The minimum detectable level of human serum chemerin was 0,5 ng/mL and detection range was 1 - 150 ng/mL. The intra- and inter-assay coefficients of variations were 5.38% and 4.13% respectively.

### Transforming growth factor beta1 level (TGF-BETA 1) measurement

Serum transforming growth factor-beta 1 levels were assessed with a commercially available quantitative enzyme linked immunosorbent assay (ELISA) kit, following the manufacturer's instructions (Ray Biotech, Georgia, United States). The minimum detect-

able level of human serum Interleukin 1 beta was 15pg/mL and the detection range was 20-60 pg/mL. The intra- and inter-assay coefficients of variations were 9.25% and 8.56% respectively.

### FMS-like tyrosine kinase 3 ligand (FLT3-Ligand) measurement

Serum FMS-like tyrosine kinase 3 ligand levels were assessed with a commercially available quantitative sandwich-enzyme-linked immunosorbent assay (ELISA) kit, following the manufacturer's instructions (R&D Systems, Minneapolis, MN, USA). The minimum detectable level of human serum FLT3-Ligand was 7 pg/mL and the detection range was 15.6 - 1.000 pg/mL. The intra- and inter-assay coefficients of variations were 7.62% and 5.28% respectively.

### Interleukin 1 beta (IL-β1) measurement

Serum Interleukin 1 beta levels were assessed with a commercially available quantitative sandwich-enzyme-linked immunosorbent assay (ELISA) kit, following the manufacturer's instructions (Bio Vendor Laboratory Medicine, Brno, Czech Republic). The minimum detectable level of human serum Interleukin 1 beta was 0.4 pg/mL and the detection range was 3.9 - 250 pg/mL. The intra- and inter-assay coefficients of variations were 3.55% and 6.12% respectively.

### Tumor necrosis factor-alpha (TNF-alpha) measurement

Serum Tumor necrosis factor-alpha levels were assessed with the commercially available quantitative sandwich-enzyme-linked immunosorbent assay (ELISA) kit, following the manufacturer's instructions (R&D Systems, Minneapolis, MN, USA). The minimum detectable level of human serum tumor necrosis factor alpha (TNF-alpha) was 5.5 pg/mL and the detection range was 15,6 - 1000 pg/mL. The intra- and inter-assay coefficients of variations were 4.45% and 8.71% respectively.

Serum total, LDL, HDL cholesterol, triglyceride, fasting glucose and urea levels were detected using enzymatic colorimetric methods on Roche Integra Biochemical analyzer with commercially available kits (Roche Diagnostics GmbH, Mannheim, Germany).

Serum hs-CRP levels were detected with *nephelometry* by using commercial reagents (Nephelometer analyzer; Behring, Marburg, Germany).

WBC and Hemoglobin values were measured *with an automated hematology* system Sysmex XT-2000i (Sysmex America Mundelein, IL).

HbA1c levels detected using an immunoturbidimetric method (Cobas Integra, Roche Diagnostics, Penzberg, Germany).

The BMI is calculated by using the equation: BMI= weight (kg)/ Height (m<sup>2</sup>).

**Assessing psoriasis severity**

The severity of psoriasis is measured with the Psoriasis Area and Severity Index (PASI) score. It is a scale that takes into account the area of lesion coverage (calculated as the percentage of the affected body surface area) as well as plaque appearance (redness, thickness and scaling). PASI values are classified as 1-10 mild, 10-20 moderate and 20 -30 severe psoriasis.

**Statistical methods**

SPSS for Windows version 18 package program was used for statistical analysis. Student t- test was used to compare the variables with normal distribution in 2 independent groups, ANOVA and LSD multiple comparison method in 2 independent groups, Mann -Whitney U test for 2 independent groups for variables with no normal distribution and Kruskal -Wallis and Dunn multiple comparison tests for 2 independent groups. The results were presented as in simple measures of percentage, mean ± standard deviation and P ≤ 0.05 was considered statistically significant.

**Results**

A total of 80 subjects were included in the study, consisting of 37 (48.25%) psoriasis patients and 43 (53.75%) healthy subjects. The psoriasis group included 18 male (48.65%) and 19 female (51.35%), and the control group included 17 male (39.53%) and 26 female (60.47%) subjects. The average age in the control group was 34.47 ± 13.40 and in the patient group was 35.16 ± 15.75 years. No significant differences were observed between the groups in terms of age (p > 0.05).

BMI values were 23.68 ± 1.60 in the control group and 26.32 ± 4.59 in the patients' group; this difference was statistically significant (p < 0.01).

When we considered the lipid profiles of patients and healthy people, the total cholesterol levels of the control group were lower than the patients' group (149.9 ± 28.61 and 206.35 ± 57.85 mg/dL respectively), this difference was statistically significant (p < 0.01). Serum LDL cholesterol levels were higher in the patients' group than the control group (132.43 ± 28.14 and 97.88 ± 14.20 mg/dL respectively), and it is statistically significant (p < 0.01). The mean serum levels of HDL cholesterol in the control and patients' group were 43.21 ± 6.55 mg/dL and 46.38 ± 8.74 mg/dL, respectively, but this difference is not statistically significant (p = 0.07). The serum triglyceride levels of the control group is lower than the psoriasis

group (121.63 ± 45.34 and 193.11 ± 204.75 respectively) and it is statistically significant (p < 0.05).

These results showed that fasting serum glucose, CRP level and serum urea concentrations were (p = 0.15, 0.2 and 0.53 respectively) and these results are not significantly different between the control and the patients' groups. The mean values of WBC were significantly higher in patient group than the control group (9.03 ± 3.31 vs 6.71 ± 1.65 10<sup>3</sup>/μL) (p < 0.01) and the HGB levels were lower in patient group (13.75 ± 1.46 vs 14.58 ± 1.95 g/dL) lower; this result was statistically different (p < 0.05). HbA1C ratios were respectively 5.96 ± 0.74% and 5.43 ± 0.82% in the patients and healthy groups, but not statistically different (p = 0.38). Clinical assessment and laboratory tests in psoriasis and the control group were showed in table 1.

Variables	Psoriasis (n = 37)	Control (n = 43)	p Value
	Mean ± SD Min - Max	Mean ± SD Min - Max	
Age(year)	35.16 ± 15.75 18 - 65	34.47 ± 13.40 18 - 65	0.41
Gender	17 Male 20 Female	21 Male 22 Female	
BMI(kg/m <sup>2</sup> )	26.32 ± 4.59 16.7 - 39.7	23.68 ± 1.60 20.7 - 29.3	<0.01
PASI score	28.19 ± 17.14 6 - 70	0 0	---
Fasting serum glucose(mg/dL)	98.95 ± 31.37 65 - 259	91.07 ± 15.56 65 - 138	0.15
Total Cholesterol (mg/dL)	206.35 ± 57.85 137 - 464	149.9 ± 28.61 88 - 195	<0.01
LDL cholesterol (mg/dL)	132.43 ± 28.14 88 - 192	97.88 ± 14.20 75 - 125	<0.01
HDL cholesterol (mg/dL)	46.38 ± 8.74 32 - 66	43.21 ± 6.55 35 - 68	0.07
Triglycerides (mg/dL)	193.11 ± 24.75 46 - 297	121.63 ± 45.34 40 - 190	<0.05
Serum Urea (mg/dL)	26.87 ± 9.25 12 - 50	25.84 ± 5.04 17.0 - 37.0	0.53
CRP (mg/dL)	12.16 ± 4.95 0.27 - 72.3	2.53 ± 1.27 0.50 - 4.50	0.2

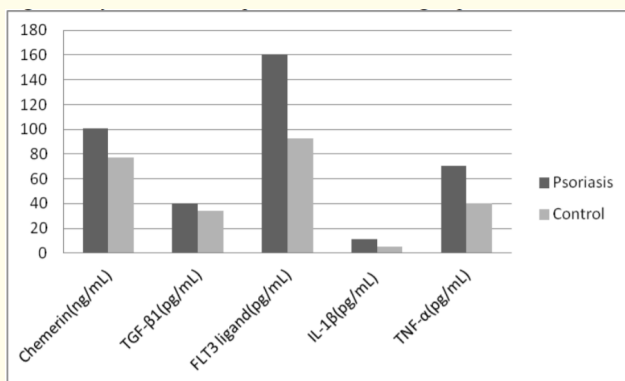
WBC (10 <sup>3</sup> /μL)	9.03 ± 3.31 5.27 - 18.94	6.71 ± 1.65 4.50 - 9.50	<0.01
HGB (g/dL)	13.75 ± 1.46 10.5 - 16.3	14.58 ± 1.95 9.6 - 19.8	<0.05
HbA1C (%)	5.96 ± 0.74 5.1 - 5.8	5.43 ± 0.82 4.3 - 6.1	0.38

**Table 1:** Clinical assessment and laboratory tests in psoriasis and the control groups.

The serum cytokine levels of patients and control group are seen in table 2 that the chemerin, TGF-β1, FLT3 ligand, IL-1β and TNF-α levels are significantly higher in psoriasis patients as compared with the control group (p < 0.01, p < 0.05, p < 0.01, p < 0.01 and p < 0.01 respectively) (Figure 1).

Cytokine	Psoriasis (n = 37) Mean ± SD Min - Max	Control (n = 43) Mean ± SD Min - Max	p Value
Chemerin (ng/mL)	100.88 ± 35.77 34.9 - 179.6	77.28 ± 19.41 38.60 - 109.3	< 0.01
TGF Beta1 (pg/mL)	40.40 ± 15.49 17.29 - 68.50	34.09 ± 11.00 14.17 - 59.45	< 0.05
FLT3 ligand (pg/mL)	160.30 ± 52.18 74.60 - 302.5	92.78 ± 20.6 57.7 - 148.6	< 0.01
IL- β1 (pg/mL)	11.58 ± 3.40 6.62 - 23.90	5.52 ± 1.65 2.31 - 8.84	< 0.01
TNF Alpha (pg/mL)	70.71 ± 30.04 20.51 - 200.96	40.42 ± 10.82 10.80 - 70.18	< 0.01

**Table 2:** Comparison of cytokine levels of patients and control group.



**Figure 1:** Cytokine levels in psoriasis and control groups.

Patients with psoriasis were graded according to their PASI scores into three subgroups (mild, moderate and severe psoriasis). Demographic and biochemical variables of the three different subgroups of psoriasis were illustrated in table 3. Although the psoriasis may be seen in all age groups, we considered that the age distribution is statistically significant different among the PASI groups of patients (p < 0.01). Mild psoriasis is more common at older ages than moderate and severe psoriasis.

Variables	Mild Psoriasis (n = 7) Mean ± SD Min - Max	Moderate Psoriasis (n = 20) Mean ± SD Min - Max	Severe Psoriasis (n = 10) Mean ± SD Min - Max	p Value
Age (years)	58.43 ± 17.90 21 - 65	29.4 ± 10.54 18 - 45	33.6 ± 10.24 18 - 58	<0.01
BMI (kg/m <sup>2</sup> )	26.39 ± 4.64 19.2 - 33.2	24.74 ± 6.4 16.7 - 39.7	27.08 ± 3.42 18.9 - 31.6	0.432
PASI score	8.57 ± 1.90 6 - 10	17.0 ± 2.36 14 - 20	40.65 ± 13.48 24 - 70	<0.01
Fasting serum glucose (mg/dL)	104.29 ± 9.38 88 - 116	102.1 ± 55.62 70 - 259	95.5 ± 18.53 65 - 161	0.772
Total Cholesterol (mg/dL)	223.29 ± 27.04 180 - 266	198 ± 51.18 139 - 283	204.6 ± 68.72 137 - 464	0.674
LDL cholesterol (mg/dL)	147.71 ± 20.41 105 - 165	129.5 ± 34.46 88 - 184	128.55 ± 26.46 94 - 192	0.286
HDL cholesterol (mg/dL)	45.71 ± 11.31 35 - 63	48.3 ± 9.97 32 - 60	45.65 ± 7.4 35 - 66	0.729
Triglycerides (mg/dL)	187.14 ± 106.97 90 - 412	169.6 ± 65.12 90 - 297	206.95 ± 270.46 46 - 1297	0.897
Urea (mg/dL)	24.91 ± 6.46 18 - 36	26.91 ± 9.17 12 - 46	35.3 ± 9.0 25.0 - 50.0	<0.05
CRP (mg/dL)	1.86 ± 1.07 0.6 - 3.45	3.22 ± 3.50 0.57 - 10.54	6.90 ± 16.28 0.27 - 72.3	0.570
WBC (10 <sup>3</sup> /μL)	8.24 ± 1.58 6.4 - 10.0	9.06 ± 2.9 6.3 - 16.60	9.29 ± 3.96 5.27 - 18.94	0.781
HGB (g/dL)	15.06 ± 1.05 14 - 17	13.7 ± 2.05 10 - 16	14.88 ± 2.05 9 - 19	0.208
HbA1C (%)	5.31 ± 0.38 4.9 - 5.9	5.56 ± 0.99 4.30 - 8	6.87 ± 4.43 4 - 25	0.447

**Table 3:** Comparison of demographic and biochemical variables of the three different subgroups of psoriasis.



We found that the BMI is seems increased proportionally to the PASI score, but there was no statistically significant difference between groups ( $p = 0.432$ ).

When we considered the lipid profiles of psoriasis subgroups, the serum total cholesterol, LDL cholesterol, HDL cholesterol and triglyceride levels were not different ( $p = 0.674, 0.286, 0.729$  and  $0.897$  respectively).

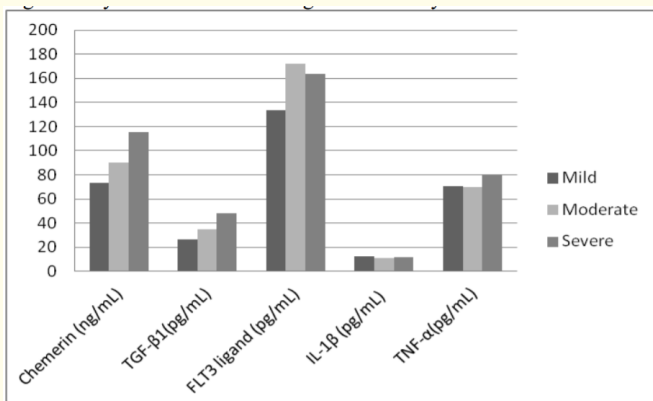
Also results showed that fasting serum glucose, CRP, WBC, HGB levels and HbA1C ratios were not significantly different between

subgroups ( $p = 0.772, 0.570, 0.781, 0.208$  and  $0.447$  respectively). But, the serum urea levels were significantly different between subgroups ( $p < 0.05$ ).

The cytokine levels of the three different subgroups of psoriasis were compared in table 4. These results showed that the serum levels of chemerin and TGF Beta 1 were higher in the severe psoriasis group and statistically significantly different ( $p < 0.01$ ). However, there was no difference in the FLT3 ligand, IL-1 $\beta$  and TNF- $\alpha$  levels between subgroups of psoriasis ( $p = 0.296, 0.869$  and  $0.724$  respectively) (Figure 2).

Cytokine	Mild Psoriasis (n = 7) Mean $\pm$ SD Min - Max	Moderate Psoriasis (n = 20) Mean $\pm$ SD Min - Max	Severe Psoriasis (n = 10) Mean $\pm$ SD Min - Max	p Value
Chemerin (ng/mL)	73.51 $\pm$ 34.35 34.9 - 138.5	90.36 $\pm$ 20.23 49.7 - 123.1	115.73 $\pm$ 35.94 58.4 - 179.6	<0.01
TGF Beta1 (pg/mL)	26.79 $\pm$ 14.13 17.72 - 57.31	34.69 $\pm$ 12.72 17.29 - 51.50	48.02 $\pm$ 12.98 26.25 - 68.50	<0.01
FLT3 ligand (pg/mL)	133.34 $\pm$ 49.12 74.6 - 200.6	172.33 $\pm$ 58.8 103.50 - 302.5	163.71 $\pm$ 49.02 99.3 - 242.3	0.296
IL- $\beta$ 1 (pg/mL)	12.07 $\pm$ 5.4 8.04 - 23.9	11.16 $\pm$ 3.36 6.62 - 18.51	11.61 $\pm$ 2.67 6.86 - 18.43	0.869
TNF Alpha (pg/mL)	70.74 $\pm$ 10.19 60.05 - 90.76	70.05 $\pm$ 10.62 40.67 - 90.97	80.02 $\pm$ 30.94 20.51 - 200.96	0.724

**Table 4:** Comparison of cytokine levels of the three different subgroups of psoriasis.



**Figure 2:** Cytokine levels according to the severity of the disease.

### Discussion

Psoriasis is a chronic inflammatory skin disease that is manifested by attacks and recovery periods. Epidemiological trials have demonstrated that psoriasis is frequently associated with metabolic syndrome, cardiovascular diseases, hypertension, diabetes, a fatty liver disease without alcohol, obesity, hyperlipidemia, inflammatory bowel disease and some psychiatric disorders. Multiple population researches have shown that there is a relation between psoriasis and other comorbid diseases and lifestyle conditions [13].

Several clinical studies in many countries have indicated that the average disease activity in psoriasis patients is higher and that the quality of life is poor even among patients seen normal by dermatologists [14].

Psoriasis can be seen at any age from birth to old age, but the most common age of onset is 30-50 years old. This study shows

that the average age of patients is  $35.16 \pm 15.75$  years, which agrees with earlier studies [15].

Altobelli, *et al.* have reported that the causes of the main chronic disease epidemics are well recognized whereas the most significant adjustable danger factors are: unhealthy food, high calorie intake; physical inactivity, tobacco, and alcohol use [16].

Our study population was not consuming tobacco or alcohol but they were sedentary and overweighted. Recent clinical studies have shown that several inflammatory molecules such as cytokines, chemokines and growth factors were appeared to have a role in the pathogenesis of psoriasis [3]. Domaa, *et al.* reported that chemerin is a newly discovered adipokine, and its expression is elevated in obesity [17].

White adipose tissue is divided into two types mainly subcutaneous fat tissue and intra-abdominal or visceral fat. The visceral fat is thought to be more metabolically active than subcutaneous adipose tissue. Actually, Panagiotakos, *et al.* clarify that obesity is associated with a state of chronic low-grade inflammation that is manifested by elevated serum concentrations of adipocytokines including chemerin [18].

An earlier study has determined that there is a sectional difference in the distribution of chemerin in the healthy and pathological skin. While chemerin is produced by keratinocytes in the healthy skin, it is downregulated in the epidermis of patients with psoriasis which is an autoinflammatory dermatosis [19].

The WBC levels of patients were higher in the patient group due to inflammation but HGB levels were lower. A previous study supports our results that reported the hematologic effects of Erythroid Differentiation Regulator 1 in inflammatory skin diseases [20].

Coban, *et al.* have demonstrated that overweight triggers inflammation that can change the levels of adipokine and cytokine. Obesity-induced inflammation may initiate immune-mediated inflammatory diseases as psoriasis [21].

In our study, we demonstrated a positive significant correlation between the serum chemerin concentrations and the BMI of patients with psoriasis ( $r = 0.514$ ,  $p < 0.01$ ). Several studies revealed that psoriasis patients are more likely to have diabetes, high cholesterol, and other "classical" risk factors for heart disease than the common people [22,23].

As shown in table 1, the total cholesterol, LDL cholesterol and triglyceride levels of patients were significantly higher than healthy

controls ( $p < 0.01$ ,  $p < 0.01$  and  $p < 0.05$ ). Although the CRP levels of the patients were measured higher out of the reference interval but not found significant differences in the psoriasis and control groups ( $p = 0.2$ ).

Deterioration of renal function is more common in psoriasis especially in patients with accompanying psoriatic arthritis that can be screened with serum urea levels of patients [24].

There was no difference in serum urea levels of patient and control group according to our results. This is probably due to the absence of patients with psoriatic arthritis in our study group. HbA1C ratios were not different within groups because we excluded the diabetic subjects at the beginning of the study, but we measured serum levels of fasting blood glucose and HbA1C ratios to neglect undiagnosed diabetes.

It is an expected result that T-cell antigen-mediated cell interactions and excessive release of certain cytokines lead to the activation of neutrophils and endothelial cells, from hyperproliferation of keratinocytes to progress of psoriatic skin lesions. It is believed that the increased levels of pro-inflammatory factors such as TGF  $\beta 1$ , FLT3 ligand, IL-  $1\beta$  and TNF- $\alpha$  in psoriasis is due to a persistent inflammatory condition that causes dysregulation of metabolic functions [21,25].

Considering the significant elevations of the chemerin, TGF  $\beta 1$ , FLT3 ligand, IL-  $1\beta$  and TNF- $\alpha$  levels in psoriasis patients was compatible with previous investigations. Similarly, the previous researchers have graded the psoriasis patients according to their psoriasis area severity index (PASI) into three groups: mild, moderate and severe psoriasis. We compared the demographic and biochemical variables of the three different subgroups of psoriasis depending on the PASI score as shown in table 3. The reviewed references have suggested that the PASI score elevates, the risk of accompanying defects like atherosclerosis, atherogenesis, hypertension, obesity, dyslipidemia, metabolic syndrome, and diabetes mellitus type 2 well increases. In our study, mild psoriasis is more common at older ages than moderate and severe psoriasis. This status is probably due to weakening immune systems with aging or effective treatment of patients. Several studies previously reported that the PASI indices of obese patients are higher than normal weighted patients [26,27].

We considered that the BMI is seems increased proportionally to the PASI score, but there was no statistically significant difference between groups. We thought that we don't have enough number of patients in severe and mild psoriasis subgroups to get

a meaningful result. Also, the lipid profiles of psoriasis subgroups, the serum total cholesterol, LDL cholesterol, HDL cholesterol and triglyceride levels were not statistically different in our study.

The serum urea levels were significantly higher in the severe psoriasis subgroup in other subgroups. But, we have not seen any studies in the literature assessing the kidney functions according to the PASI index of psoriasis patients.

When we compared the cytokine levels of the three different subgroups of psoriasis, the serum levels of chemerin and TGF- $\beta$ 1 were higher in the severe psoriasis group than the others. On the other hand the FLT3 ligand, IL- 1 $\beta$  and TNF- $\alpha$  levels were not different.

Guzel., *et al.* have determined a strong positive correlation between the PASI score and the chemerin levels. They suggest that the chemerin levels indicate that there is an inflammatory process in psoriasis and this indication is a useful to signal of the risk of psoriasis [6].

In the current study, the severity of psoriasis is correlated positively with the serum chemerin concentrations ( $r = 0.695$ ,  $p < 0.01$ ). It is an expected conclusion, the chemerin is important in the skin inflammation process because it expresses with high levels secreted in the human epidermis. Increased levels of chemerin leads to proliferation of chemR23-expressing DCs in psoriatic skin to support many anti-bacterial activities. The chemerin may contribute to skin defense by increasing the involvement of DCs in the process or by acting as an anti-bacterial agent in the epidermis [28].

CRP is a prominent pro-inflammatory molecule member of the pentraxin family, mainly produced by hepatocytes and its production is controlled with certain cytokines, especially IL-6 and IL-17. Chronic immune-mediated inflammatory diseases are highly effective on serum CRP levels. In our study, increased levels of serum CRP in patients with active psoriasis were noticed, and confirming the previous reported studies [29].

Our results showed that the CRP is positively correlated with serum chemerin levels and PASI scores ( $r = 0.515$ ,  $p < 0.01$  and  $r = 0.425$ ,  $p < 0.01$ ).

Since TGF- $\beta$ 1 is a potent growth inhibitor for human keratinocytes, the lack of down-regulation may be important for the pathogenesis of psoriasis. High plasma TGF- $\beta$ 1 levels due to inflammation have been shown to be associated with the severity of psoriasis and are therefore suggested to be useful in assessing disease severity [30].

The current study supported previous studies as plasma levels of TGF- $\beta$ 1 are strongly associated with psoriasis severity and therefore can be considered as a possible biomarker for the assessment of disease activity.

In this study, we demonstrated that the FLT3 ligand levels were significantly higher in psoriasis than in the control group. However, there was no correlation between the FLT3 ligand concentrations and the severity of the disease. Thus, it has been demonstrated that the FLT3 ligand plays a critical role in regulating the generation and maturation of DCs. The inhibition of FLT3 signaling could induce apoptosis in human DCs [31,32].

We have not found an association between psoriasis severity and IL- 1 $\beta$  levels, but earlier studies reported statistically significant results [33].

Clara De Simone., *et al.* reported that TNF- $\alpha$  is derived from active dendritic cells, Th1 cells, Th17 cells and keratinocytes. Anti-TNF- $\alpha$  agents are currently used in the treatment of psoriatic patients. No correlation was found between psoriasis severity and TNF- $\alpha$  levels in the present study [34].

In psoriasis, autoreactive T cells are improperly activated, thus T cells were targeted for suppression of the immun system in treatment. DCs are the major antigen presenters in the regulation of immune responses and potent activators of T-cells. Interactions between DC and T cells may cause differentiation of T-cells to specific phenotypes. This connection plays an important role in the pathogenesis of autoimmune diseases, leading to the secretion of cytokines, including TGF- $\beta$ 1, FLT3 ligand, IL- 1 $\beta$  and TNF- $\alpha$  [35].

Taken together, our results suggested that chemerin, TGF- $\beta$ 1, FLT3 ligand, IL- 1 $\beta$  and TNF- $\alpha$  are likely potential molecular targets for the treatment of psoriasis through interference with DCs and leading to increasing their level in psoriasis patients.

One main limitation of the present study is that it would have been more interesting if we had measured other inflammatory mediators. We thought that we don't have enough number of patients in severe and mild psoriasis subgroups to get a meaningful result. Also, this is a cross-sectional correlational study, which does not allow to make firm inferences on causal associations.

## Conclusion

Both obesity and psoriasis are chronic diseases that require high-cost treatment and affect the quality of life. It has been reported [11] that improving obesity also psoriasis improves. Our study



aimed to evaluate if psoriasis patients with an elevated BMI do also have and increased PASI. The originality of our study is that psoriasis severity, in terms of PASI, was more statistically significant between overweight and norm weight patients than between obese and norm weight patients. These results highlight the importance of considering PASI and BMI together and the qualified dermatologist has to face the fact that in treating psoriasis attention has to be paid also to “weight gain” and to select treatments that do not contribute (or worsen) the tendency to increase BMI.

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### Conflict of Interest

The authors have no conflict of interest with any commercial or other association in connection with the submitted article.

### Author’s Contributions

All the contributing authors have participated in the preparation of the study.

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