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Role of GDF-15 as an inflammatory marker in patients with psoriasis vulgaris

Psoriazisli hastalarda inflamatuvar marker olarak GDF-15'in rolü

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Abstract

Background and Design: Psoriasis is a chronic, inflammatory disease, and several biochemical markers play role in its inflammatory process. This study measured the levels of interleukin-12 (IL-12), IL-17a, IL-22 and IL-23, high-sensitivity C-reactive protein (hs-CRP), tumor necrosis factor-alpha (TNF-α) and serum growth differentiation factor-15 (GDF-15) and aimed to detect the relationship of serum GDF-15 level with inflammation and disease severity.
Materials and Methods: This study included 50 consecutive patients diagnosed with plaque-type psoriasis. For all patients, dermatological examinations were performed, and psoriasis area severity index (PASI) scores were recorded. Patients with PASI <10 were considered to have mild (group 1), 10-20 moderate (group 2), and >20 severe (group 3) psoriasis.
Results: No difference was observed between the patient and the control groups in terms of age, sex, IL-17a and IL-22. A statistically non-significant difference was detected in terms of IL-12 and IL-23. However, there was significant difference between two groups in terms of hs-CRP, TNF-α and GDF-15. GDF-15 was significantly different in all three groups (p<0.001). A significant correlation was observed between PASI score and disease duration (p=0.005), hs-CRP (p=0.003), TNF-α (p=0.002), and serum GDF-15 levels (p<0.001). The serum GDF-15 level that can predict a high PASI score was >1498.5 pg/mL (area under the curve: 0.813, p<0.001) in the receiver operating characteristic curve analysis. This study is mainly limited by the lack of follow-up and pre- and post-treatment assessment. Inflammatory markers were measured only in the serum, and their tissue levels are unknown.
Conclusion: In addition to PASI score, GDF-15 levels can be a guide in monitoring treatment and systemic inflammation, determining the disease severity, and providing efficient treatment.
Keywords: Psoriasis vulgaris, PASI, GDF-15

Öz

Amaç: Psoriazis kronik inflamatuvar bir hastalıktır ve inflamasyon sürecinde çeşitli biyokimyasal belirteçler rol oynar. Çalışmamızda interlökin-12 (IL-12), IL-17a, IL-22 ve IL-23, yüksek-sensitif C-reaktif protein (hs-CRP), tümör nekroz faktörü-alfa (TNF-α) ve serum büyüme farklılaşma faktörü-15 (GDF-15) düzeylerini ölçtük ve serum GDF-15'in inflamasyon ve hastalık şiddeti ile ilişkisini saptamayı amaçladık.
Gereç ve Yöntem: Çalışmamıza plak tipi psoriazis tanısı ile 50 ardışık hasta dahil edildi. Tüm hastalar için dermatolojik incelemeler yapıldı ve psoriazis alan şiddet indeksi (PAŞİ) skorları kaydedildi. PAŞİ'si 10'un altında olan hastalar hafif (grup 1), 10 ila 20 arasında orta (grup 2) ve 20'den fazla şiddetli (grup 3) olarak kabul edildi.

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Bulgular: Hasta ile kontrol grubu arasında yaş, cinsiyet, IL-17a ve IL-22 açısından herhangi bir fark izlenmedi. IL-12 ve IL-23 açısından ise istatistiksel olarak anlamlı olmayan farklılık izlendi. Fakat hs-CRP, TNF-α ve GDF-15 açısından ise iki grup arasında anlamlı farklılık mevcuttu. GDF-15'in 3 grupta da anlamlı olarak farklı olduğu bulundu (p<0,001). PAŞİ skoru ile hastalık süresi (p=0,005), hs-CRP (p=0,003), TNF-α (p=0,002) ve serum GDF-15 düzeyleri (p<0,001) arasında anlamlı bir korelasyon gözlendi. Ciddi PAŞİ skorunu öngörebilen serum GDF-15 düzeyleri de alıcı işletim karakteristiği analizinde >1498,5 pg/mL (eğri altında kalan alan: 0,813, p<0,001) olarak bulundu.
Sonuç: PAŞİ skoruna ek olarak, GDF-15 düzeylerinin tedavi ve sistemik inflamasyonun izlenmesinde, hastalığın şiddetinin belirlenmesinde ve etkili tedavinin sağlanmasında bir rehber olabileceğini düşünüyoruz.
Anahtar Kelimeler: Psoriazis vulgaris, PAŞİ, GDF-15

Introduction

Psoriasis is a chronic, inflammatory disease characterized with silver-white squams localized on sharply circumscribed, erythematous plaque or papules[1]. Psoriasis is usually characterized with symmetric lesions localized on the scalp and extensor surfaces of the knee, elbow, sacral region, and joints. While the exact cause of psoriasis is unknown, genetic and environmental factors play important roles in disease development[2,3].

Several biochemical markers play a role in the inflammation process in psoriasis vulgaris. Previous studies have demonstrated that markers including tumor necrosis factor-alpha (TNF-α), interleukin-12 (IL-12), IL-23, IL-17, and IL-22 are involved in the etiology of psoriasis[4-7].

Growth differentiation factor-15 (GDF-15) is a biochemical marker, and its blood level increased with inflammation. Despite its similarities to inflammatory cytokines, it also possesses independent, specific biological roles[8]. As a newly demonstrated inflammation marker, GDF-15 has been demonstrated to be used as a possible inflammation marker in cardiovascular diseases, kidney diseases, hematopoietic diseases, and cancers[9-12]. While many studies have explored the relationship between the level of inflammation and disease severity in patients with psoriasis, no study on serum GDF-15 level was performed to date. Thus, in the present study, we aimed to detect the relationship of this cytokine with inflammation and disease severity.

Materials and Methods

This study included 50 consecutive patients who were admitted to the Dermatology and Venereal Diseases Outpatient Clinic, Namık Kemal University Training and Research Hospital, and diagnosed with clinical and/or histopathological plaque-type psoriasis from December 2015 to December 2016. The control group consisted of 30 volunteers without any disease. The exclusion criteria were as follows: age outside 18-65 years, diabetes mellitus, cancer, chronic renal failure, active infection, chronic liver diseases, cardiovascular diseases, and chronic rheumatic diseases, which may worsen inflammation. Patients who used any type of systemic treatment for psoriasis vulgaris within the last 3 months were also excluded.

This study was performed with the approval of the Medical Ethics Committee Namık Kemal University Training and Research Hospital (approval number: 2015/124/11/07, date: 10.12.2015), and funded by the Department of Namık Kemal University Scientific Research Projects Commission. All patients were informed regarding the study content, and they gave written consent.

Patients' data regarding age, sex, disease duration, and systemic and topical treatments used within the last 3 months were collected. For all patients, dermatological examinations were performed, and psoriasis area severity index (PASI) scores were recorded.

Calculation of PASI scores

PASI scores were calculated before the study. Patients with PASI of <10 were considered to have mild (group 1), 10–20 moderate (group 2), and >20 severe (group 3) disease.

Assessment of laboratory parameters

Following collection of blood samples, they were kept at -80 °C until analysis. In the collected serum samples, levels of GDF-15 (Lot no.: E16-063S14, BioVendor, Modrice, Czech Republic), high-sensitivity C-reactive protein (hs-CRP) (Lot no: X16-087, Modrice), TNF-α (Lot no: 125939027, Platinum, eBioscience, Austria), IL-12 (Lot no: 130236050, Platinum, eBioscience), IL-17 (Lot no: 123793019, Platinum, eBioscience), IL-22 (Lot no: 127160019, Platinum, eBioscience), and IL-23 (Lot no: 125023007, Platinum, eBioscience) were measured using enzyme-linked immunoassay according to the instructions of the corresponding companies. ROBONIK micro ELISA (Unitron Bio Medicals, India) and DYNEX automated micro ELISA devices (Dynex Technologies Inc., VA, USA) were used for the assessments.

Statistical Analysis

Statistical analyses were performed using SPSS (version 18, IBM Corp., Armonk, NY, USA) and Medcalc (version 12.7.8, Mariakerke, Belgium) package software. Continuous variables were expressed as mean ± standard deviation and categorical variables as percentage. The Shapiro-Wilk test was performed to determine whether the continuous variables are distributed normally. For inter- and intra-group comparisons, t-test, One-Way analysis of variance (ANOVA), or Kruskal-Wallis test was used. For correlation analysis, Pearson's or Spearman's correlation test was performed. To determine the independent variables affecting the PASI score, multilinear regression analysis was performed. After univariate analysis, p-values of <0.25 were taken to the regression analysis. The receiver operating characteristic curve (ROC) analysis was performed to determine the GDF-15 value that can be used to predict the severity of PASI score, and p value <0.05 was regarded as significant.

Results

Demographic and laboratory characteristics of the study population are shown in Table 1. The mean disease duration was 9.5±6.7 years, and mean PASI score was 10.9±7.8 points. No difference was observed between the patient and control groups in terms of age, sex, and levels of IL-17a and IL-22 (p>0.05). No significant difference was detected in the levels of IL-12 (p=0.054) and IL-23 (p=0.086). However, significant difference was found between the two groups in terms of hs-CRP (p<0.001), TNF-α (p=0.007), and GDF-15 (p=0.003) levels.

The intra-group comparison of the patient group is shown in Table 2. No difference was detected between the groups in terms of IL-12, IL-17a, IL-22, and IL-23 levels (p>0.05). A significant difference was only observed between group 1 and group 3 in terms of hs-CRP and TNF-α (p<0.05), and GDF-15 levels were significantly different in all three

groups (p<0.001).

A significant correlation was observed between PASI score and disease duration (r=0.389, p=0.005), hs-CRP (r=0.415, p=0.003), TNF-α (r=0.426, p=0.002), and serum GDF-15 levels (r=0.579, p<0.001). Significant correlation was also found between disease duration with hsCRP (r=0.284, p=0.046) and GDF-15 (r=0.314, p=0.026).

To determine the independent variables affecting the PASI score, multilinear regression analysis was performed. Based on the analysis, TNF-α (p=0.002) and GDF-15 (p=0.002) levels were detected to be independent predictors in determining the severity of PASI score (Table 3).

The ROC curve analysis was performed into two individual models to determine the GDF-15 value that can be used to predict the severity of the PASI score. In model 1, the GDF-15 value that can predict a moderate PASI score was >1120.5 pg/mL with 84.6% sensitivity and 70.8% specificity [area under the curve (AUC): 0.821, 95% confidence interval (CI) 0.686-0.915, p<0.001]. In model 2, the GDF-15 level that can predict a high PASI score was >1498.5 pg/mL with 77.8% sensitivity and 73.2% specificity (AUC: 0.813, 95% CI 0.678-0.909, p<0.001) (Figure 1).

Discussion

Table 1. Demographic and laboratory characteristics of the study population

	Control group (n=32)	Patient group (n=50)	p
Age, years	40.0±12.7	41.0±13.1	0.707
Gender (male; n, %)	19 (38%)	31 (62%)	0.294
hs-CRP, µg/mL	3.0±2.5	6.8±5.4	**<0.001**
IL-12, pg/mL	10.7±4.1	12.9±5.3	0.054
IL-17a, pg/mL	0.5±0.5	0.7±0.8	0.225
IL-22, pg/mL	35.4±28.1	40.1±21.5	0.393
IL-23, pg/mL	32.2±8.1	38.9±20.8	0.086
TNF-α, pg/mL	0.9±0.8	1.8±1.9	**0.007**
GDF-15, pg/mL	987.8±401.9	1495.0±861.4	**0.003**
PASI score	10.9±7.8	-	-
Disease duration, years	9.5±6.7	-	-

hs-CRP, High-sensitive C-reactive protein, IL: Interleukin, GDF: Growth differentiation factor, PASI: Psoriasis area and severity index, TNF-α: Tumor necrosis factor-alpha

Psoriasis is a genetic, chronic, inflammatory, and hyperproliferative skin disease. While its etiopathogenesis requires further explanation, it causes significant inflammatory changes in both the dermis and epidermis[13]. Although psoriasis is becoming known as a T-lymphocyte-mediated disease, it is not regulated by a single group of cells and occurs as a result of complex interactions of dendritic cells, macrophages, mast cells, neutrophils, and keratinocytes.

In the most recent studies, psoriasis occurs in individuals with genetic predisposition as a result of triggering environmental factors such as emotional stress, trauma, and infection. Moreover, keratinocyte proliferation is not the main pathology, and it actually occurs secondary to many pro-inflammatory cytokines including interferon-gamma, TNF-α, IL-1, IL-2, IL-6, IL-12, IL-17a, IL-22, and IL-23 released from T-cells, which infiltrated the skin against antigenic stimulant[13,14]. By showing the activation of the inflammatory process, these markers are important to monitor the clinical course, assess the severity, and form treatment strategies for the disease.

Given its key role in the pathogenesis of psoriasis, TNF-α is also actively involved in the initiation of inflammatory response and induction keratinocyte proliferation by increasing the release of various growth factors and adhesion molecules[4]. Many studies exploring the relationship of TNF-α levels with psoriasis severity and activation have yielded contradictory results. In their study of 62 patients with psoriasis, Xuan et al.[15] found higher serum TNF-α levels in the patient group than

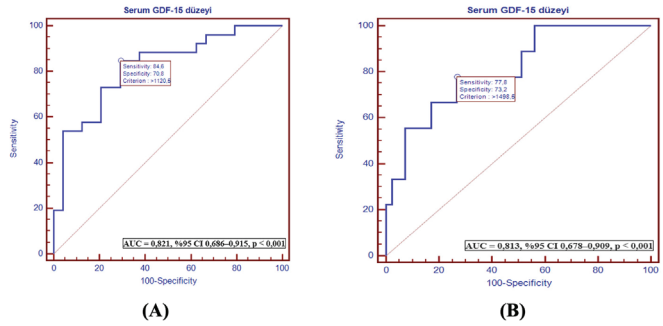

Figure 1. Receiver operating characteristics curve of serum GDF-15 value predicting moderate **(A)** (AUC: 0.821, 95% CI 0.686-0.915, p<0.001) and high **(B)** PASI score (AUC: 0.813, 95% CI 0.678-0.909, p<0.001)

GDF-15: Growth differentiation factor, AUC: Area under the curve, CI: Confidence interval, PASI, Psoriasis area and severity index, ROC: Receiver operating characteristic

Table 2. Laboratory characteristics of the patients

	Group 1 (n=24)	Group 2 (n=17)	Group 3 (n=9)	p (ANOVA)
PASI score	4.1±1.8	13.6±1.9	23.9±3.0	**<0.001¥.£.***
hsCRP, µg/mL	4.7±4.1	7.7±5.5	10.7±6.4	**0.011£**
IL-12, pg/mL	12.0±4.1	12.8±4.9	15.3±8.4	0.298
IL-17a, pg/mL	0.6±0.7	0.8±1.1	0.9±0.6	0.595
IL-22, pg/mL	34.7±15.8	45.0±27.5	45.2±20.8	0.234
IL-23, pg/mL	39.0±21.0	41.8±22.5	33.6±17.7	0.639
TNF-α, pg/mL	1.1±1.5	2.2±1.9	3.2±2.1	**0.009£**
GDF-15, pg/mL	1046.0±490.6	1658.1±715.4	2384.3±1130.6	**<0.001¥.£.***

¥: p<0.05 between group 1 and group 2, £: p<0.05 between group 1 and group 3, *: p<0.05 between group 2 and group 3, hs-CRP: High-sensitive C-reactive protein, IL: Interleukin, GDF: Growth differentiation factor, PASI: Psoriasis area and severity index, TNF-α: Tumor necrosis factor-alpha

Table 3. Multivariate linear regression analysis showing laboratory parameters for predicting PASI score

	B	95% CI	p
IL-22	-0.009	-	0.834
hs-CRP	0.189	-	0.343
TNF-α	1.576	0.633-2.519	**0.002**
GDF-15	0.004	0.002-0.007	**0.002**

hs-CRP: High-sensitive C-reactive protein, IL: Interleukin, GDF: Growth differentiation factor, TNF-α: Tumor necrosis factor-alpha

in healthy group and thought this result is caused by the potential presence of specific inflammatory cytokines in psoriasis. Sereflican et al.[16] detected a serious correlation between serum TNF-α levels and PASI score. Ragab et al.[17] found higher serum TNF-α levels in patients with severe psoriasis than in patients with mild-moderate psoriasis. In the present study, serum TNF-α levels were higher in the psoriasis patient group than in the healthy control group, and a significant correlation was found between serum TNF-α levels and PASI score.

Both IL-12 and IL-23 have important roles in continuing inflammation and abnormal keratinocyte proliferation in psoriasis. IL-23 triggers IL-17 release by stimulating Th-17 cells, and IL-17 causes epidermal keratinocyte proliferation in psoriasis[18]. IL-22 regulates the communication between the immune system and epithelial cells, leads to epidermal hyperplasia and hypogranulosis, and activates pro-inflammatory response by causing the release of cytokines, chemokines, and acute phase proteins from cells[19]. Many studies have examined serum levels of IL-12, IL-17a, IL-22, and IL-23 in patients with psoriasis. Roussaki-Schulze et al.[20] found higher serum IL-12 levels in the psoriasis patient group than in the control group. On the contrary, Jacob et al.[21] reported low IL-12 levels in patients with psoriasis. In a study assessing serum IL-17 levels in patients with psoriasis, while serum IL-17 levels were not high in the patient group, a significant correlation was found between IL-17 and PASI (10). Yilmaz et al.[22] examined serum IL-17 levels in patients with severe psoriasis (PASI >10) and patients with pustular psoriasis and detected a correlation with PASI score. Meephansan et al.[23] found high serum IL-22 levels in patients with psoriasis and a significant correlation with disease severity. Sobhan et al.[6] did not find any difference in serum IL-22 levels between the psoriasis patient group and the control group, but they detected a considerable correlation between disease severity and IL-22 and highlighted the clinical importance of IL-22 in patients with psoriasis. Ma et al.[24] found that the serum IL-23 levels were significantly higher in their psoriasis patient group than in the healthy control group. In the recent preliminary report of their study in 55 patients with plaque-type psoriasis, Brito-Luna et al.[7] did not find any difference between the patient and control groups in terms of IL-22 and IL-23 levels. Moreover, they did not report any correlation between cytokine levels and PASI score[7].

In our study, in our evaluation of the IL-12, IL-17a, IL-22, and IL-23 levels, they tend to be higher in the patient group, and the difference did not reach significance. However, in the intra-group evaluation of the patient group, no difference was detected, and no correlation was observed between PASI score and disease duration between the subgroups. Our results appear to contradict the currently accepted paradigms for the immunopathogenesis of psoriasis. This might be due to the small number of patients. Therefore, we think that larger studies are needed to clarify this.

TNF-α induced IL-6 has been shown to increase hepatic production and serum levels of the acute phase reactant CRP in psoriatic patients[25]. Hs-CRP assessment allows detection of very low levels of CRP, which cannot be detected by conventional methods[26]. To date, many studies on hs-CRP in patients with psoriasis have obtained contradictory results. Emre et al.[27] did not find any significant relationship between the patients' CRP and hs-CRP levels, and PASI scores. Gkalpakiotis et al.[28] detected higher hs-CRP levels in the patient group than in the control group, and no relationship with PASI score was detected. Similarly, Balta et al.[29] detected high hs-CRP levels in the patient population. In our study, we found higher serum hs-CRP levels in the patient group than in the control group. Moreover, a significant correlation was found between serum hs-CRP levels and both PASI score and disease duration. We believe that our results are consistent with the etiopathogenesis of psoriasis, which is a chronic inflammatory disease, and support the literature.

As GDF-15 is known as macrophage inhibitor cytokine-1 until recently, it is a member of transforming growth factor-beta (TGF-β) family[30] and found in various cells (macrophages, vascular smooth muscle cells, adipocytes, cardiomyocytes, endothelial cells, and fibroblasts), tissues (adipose, vascular, and central and peripheral nervous systems), and organs (heart, brain, and liver) involved in inflammatory response, growth, and cell differentiation[8]. Conditions triggering GDF-15 production include biomechanical stress, ischemia, hypoxia, inflammatory cytokines (TNF-α, IL-2, and IL-6), angiotensin II, macrophage colony-stimulating factor, and TGF-β. In the literature, the most comprehensive investigations on the clinical use of GDF-15 are in the cardiovascular field[9,31].

To date, serum GDF-15 level in some rheumatic diseases has been studied. Brown et al.[32] assessed serum GDF-15 levels in patients with rheumatoid arthritis, and they found high GDF-15 levels in the patient group and a correlation with disease severity. Moreover, Meadows et al.[33] found high levels of GDF-15 in patients with systemic sclerosis accompanied by pulmonary arterial hypertension. They reported that GDF-15 >125 pg/mL is associated with decreased survival. In another study in patients with Behçet's disease[34], while no difference was observed in GDF-15 levels between the patient group and the control group, high serum levels were detected in the peripheral arthritis subgroup. In our study, patients with psoriasis had higher GDF-15 levels than the normal healthy population. We also detected a strong correlation between disease duration and PASI score. In our analyses of determining a GDF-15 cut-off value that can predict the severity of PASI score, we found that serum GDF-15 level >1498.5 pg/mL may predict a high PASI score. Despite the limited data regarding serum GDF-15 levels in chronic rheumatic diseases, our results are consistent with the historical findings in patients with psoriasis in which the inflammatory process has a key role in etiopathogenesis.

Study Limitations

The number of participants included in our study was relatively low. Patients were not followed up, and no pre- and post-treatment assessment was performed with the use of some kinds of treatment. Inflammatory markers were also measured only in the serum, and their tissue levels are unknown. For further clarification of the relationship between psoriasis severity and GDF-15, more comprehensive studies are needed, including psoriasis and other inflammatory skin diseases

with more patients and control subjects and assessing pre- and post-treatment GDF-15 levels.

Conclusion

Consequently, in patients with psoriasis, a chronic inflammatory disease, we found high levels of serum hs-CRP, TNF-α, and GDF-15, which are indicators of increased inflammation and cellular immune response. Additionally, we detected a strong correlation between these markers and both disease duration and disease severity. In addition to PASI, we believe that GDF-15 levels can be a guide in monitoring treatment and systemic inflammation, determining disease severity, and providing efficient treatment.

Ethics

Ethics Committee Approval: This study was performed with the approval of the Medical Ethics Committee Namık Kemal University Training and Research Hospital (approval number: 2015/124/11/07, date: 10.12.2015).

Informed Consent: It was obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.K.T., M.E.Y., G.E., Concept: M.K.T., M.E.Y., G.E., Design: M.K.T., G.E., Data Collection or Processing: M.K.T., G.E., O.R., H.A., Analysis or Interpretation: M.K.T., G.E., O.R., M.E.Y., Literature Search: M.K.T., O.R., H.A., Writing: M.K.T., G.E., M.E.Y.

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

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