ÖZGÜN ARAŞTIRMA ORIGINAL RESEARCH

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COULD GROWTH DIFFERENTIATION FACTOR-15 BE A NEW INFLAMMATORY PATHWAY IN PSORIASIS VULGARIS?

BÜYÜME FARKLILAŞMA FAKTÖRÜ-15 PSORİASİS VULGARİSTE YENİ BİR İNFLAMATUVAR YOLAK OLABİLİR Mİ?

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Öz

Amaç
Psoriasis vulgaris kronik inflamatuvar bir hastalık olup, etyopatogenezde T hücrelerin önemli rol oynadığı inflamatuvar mekanizmalar rol almaktadır. Son yıllarda psoriasisin sadece deriye sınırlı olmayıp aynı zamanda bazı komorbiditeler ile ilişkili olduğu gösterilmiştir. Büyüme farklılaşma faktörü-15 (GDF-15), dönüştürücü büyüme faktörü beta süper ailesinin (TGF-ß) bir üyesidir ve inflamasyonla artmaktadır. Bu çalışmada; serum GDF-15 düzeyi ve bunun hastalığın etyopatogenezinde rolü olduğu düşünülen tümör nekrozis faktör alfa (TNF-α) ve diğer metabolik parametrelerle arasındaki ilişkinin değerlendirilmesi amaçlandı.

Gereç ve Yöntem
Çalışmaya 41 psoriasis vulgarisli hasta ve 41 sağlıklı kontrol dahil edildi. Tüm katılımcıların dermatolojik muayenesi yapıldı ve psoriasis alan ve şiddet indeksi (PAŞİ) skoru hesaplandı. Tüm katılımcıların boy, kilo ölçümleri, sistolik ve diastolik kan basınçları, bel ve kalça çevreleri, lipit profilleri, biyokimyasal parametreleri değerlendirildi. Serum GDF-15 ve TNF-α düzeyleri ELİSA yöntemi ile ölçüldü.

Bulgular
Hasta ve kontrol grubu arasında yaş, cinsiyet, lipit profilleri, biyokimyasal parametreler ve yüksek-sensitif C-reaktif protein (hs-CRP) düzeyleri açısından anlamlı fark gözlenmedi. Hasta grubunda kontrol grubuna kıyasla serum GDF-15 ve TNF-α düzeyleri anlamlı derecede yüksek bulundu ($p<0.001$ ve $p=0.015$). GDF-15 ve TNF-α düzeyleri arasında pozitif korelasyon saptandı ($r=0.455$, $p=0.04$).

Sonuç
GDF-15'in psoriasiste özellikle TNF-α ile ilişkili inflamatuvar yolakta rolü olabileceğini düşünmekteyiz.

Anahtar Kelimeler: GDF-15, İnflamasyon, Komorbidite, Psoriasis

Abstract

Objective
Psoriasis vulgaris is a chronic inflammatory disease, in which T cells play an important role in the etiopathogenesis and inflammatory mechanisms. Growth differentiation factor (GDF) 15 is a member of the transforming growth factor beta superfamily (TGF-ß), which increases with inflammation and has

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various cell regulatory functions. In this study; it was aimed to evaluate the relationship between serum GDF-15 level and tumor necrosis factor alpha (TNF-α), which is thought to have a role in the etiopathogenesis of the disease, and other metabolic parameters.

Material and Method
Forty-one patients with psoriasis vulgaris and 41 healthy controls were included in the study. Dermatological examination of all patients was performed and the psoriasis area severity index (PASI) score was calculated. Height and weight measurements, systolic and diastolic blood pressures, waist and hip circumferences, lipid profiles, and biochemical parameters of the patients were evaluated. Serum GDF-15 and TNF-α levels were measured by the ELISA method.

Results
There was no significant difference between the patient and control groups in terms of age, gender, lipid profiles, biochemical parameters and high-sensitivity C-reactive protein (hs-CRP) levels. Serum GDF-15 and TNF-α levels were found to be significantly higher in the patient group compared to the control group ($p<0.001$ and $p=0.015$). A positive correlation was found between GDF-15 and TNF-α levels ($r=0.455$, $p=0.04$).

Conclusion
We think that GDF-15 may have a role in psoriasis, especially in the inflammatory pathway associated with TNF-α.

Keywords: Comorbidity, GDF15, Inflammation, Psoriasis

Introduction

Psoriasis is a chronic disease that is frequently seen in the population and progresses with attacks and remissions. It is thought that mainly T cell-mediated mechanisms play a role in its etiopathogenesis, and the importance of cytokines such as TNF-α, IL-6, IL-17, IL-23 and IFN-γ has been demonstrated (1, 3). However, it is still being investigated whether the disease is an autoimmune disease caused by reactivity to self-antigens or an immune activation caused by exogenous or endogenous stimuli. Studies have shown that the frequency of metabolic syndrome (MetS) with central obesity, hypertension, dyslipidemia and glucose intolerance increases in patients with psoriasis. Among the inflammatory cytokines, especially TNF-α, had an important role in the relationship between psoriasis and MetS (3).

GDF-15 is a cytokine that plays a role in cell regeneration, has anti-apoptotic effects and increases during inflammation. Its level is thought to rise in obese patients and is related with cardiometabolic risk (4, 5). It was previously shown that the gene expression and serum level of GDF-15 are high in psoriasis patients and were thought to be associated with disease severity (6). It has been known that psoriasis has been associated with diseases such as obesity and metabolic syndrome in recent years, and the risk of developing cardiovascular diseases also increases in this disease (7). However, how and by which mechanism these comorbidities occur is still under investigation. Therefore, in this study, it was intended to evaluate serum GDF-15 and TNF-α levels in psoriasis vulgaris and to search their relationship with metabolic, clinical and biochemical parameters, unlike previous studies.

Material and Method

This study received permission from the Local Ethics Committee (Number: 294). Forty-one psoriasis vulgaris (mean age: 40.24±14.07 years; 23 males, 18 females) and 41 healthy individuals (mean age: 39.64 ±12.53 years; 22 males, 19 females) were included in the study. The diagnosis of psoriasis vulgaris was made by evaluating the clinical findings and/or skin biopsy. The severity of the disease in the patient group was evaluated with the Psoriasis Area and Severity Index (PASI) score calculated by skin examination. A PASI score of <10 was assessed as mild, while scores ≥10 were classified as moderate and severe psoriasis (8).

Patients older than 18 years of age, who were diagnosed with psoriasis clinically and/or histopathologically, had no systemic treatment (systemic retinoid, systemic steroid, cyclosporin, methotrexate, biologic agents, and phototherapy), for psoriasis for the last 3 months, topical treatment for psoriasis for the last 1 month, no nonsteroidal anti-inflammatory drug use in the last 1 week, and no inflammatory disease other than psoriasis were included in the study.

Participants with renal failure, diabetes mellitus, infection, pregnancy, malignancy, connective tissue disease were excluded from the study.

Gender, height, weight, age, body mass index (BMI: body weight (kg)/height m2), waist circumference , hip circumference, systolic and diastolic blood pressures of all participants were recorded.

Biochemical Measurements

After at least 8 hours of fasting, venous blood samples were collected and serum samples were collected by centrifugation at 3000 rpm for 10 minutes. Fasting blood glucose (FBG), lipid profile, C-reactive protein (hs-CRP), insulin levels were analyzed. Serum GDF-15 and TNF alpha levels were measured by ELISA method (EL-H0080 Elabscience, Wuhan, Hubei Province, China). For homeostatic model assessment of insulin resistance (HOMA-IR) calculation HOMA-IR= insülin*glucose/405 formula was used (9).

Statistical Analysis

SPSS 18 program (Version 18.0. Chicago: SPSS Inc) was used for statistical analysis of all data in the study. The normality of the variables was evaluated with the Kolmogorov-Smirnov test. Student's t test was used to compare the variables with normal distribution, and the Mann-Whitney U test was used for non-normal distributed variables. The relationship between GDF-15, TNF-α and other distributed variables in psoriasis vulgaris patients was evaluated by Spearman correlation test. Descriptive analyzes were presented as mean±standard deviation (SD) and median (IQR). A p value of <0.05 was considered significant.

Results

There was no significant difference between the groups in terms of age and gender (p > 0.05 for all). The mean duration of psoriasis vulgaris was 9±11 years. Arthritis was accompanied in 15 (36.6%) of the patients, and nail involvement in 17 (41.5%). The mean PASI score of the patients was 11.96±7.45. BMI, LDL-C, TG, hs-CRP, and FBG levels showed no difference between the groups (p>0.05). Descriptives, clinical and laboratory characteristics of the study groups are shown in Table 1. Compared to the healthy control group, psoriasis patients had significantly higher serum GDF-15 and TNF-α levels (p<0.001, p=0.015, respectively) (Figure 1 and 2).

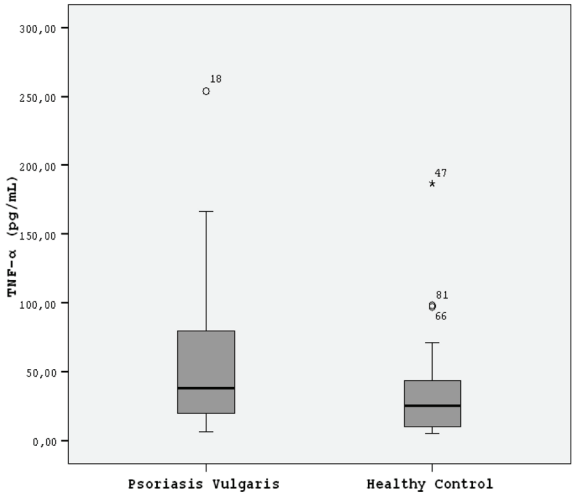

Figure 2
TNF-α levels in study groups

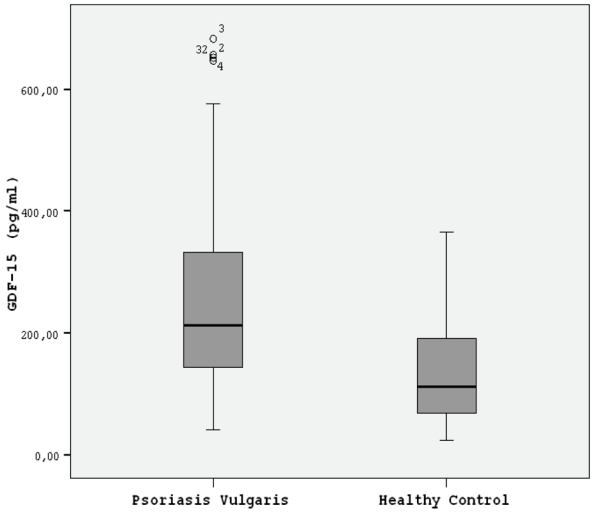

Figure 1
GDF-15 levels in study groups

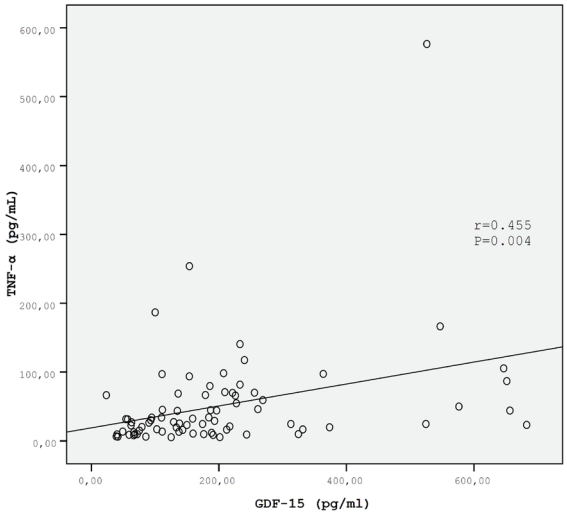

Figure 3
Correlation analysis between GDF-15 and TNF-α

Table 1 Descriptives, clinical and laboratory characteristics of the psoriasis vulgaris and healthy controls

	Psoriasis vulgaris	Healthy controls	p
Gender Female,n (%) Male, n (%)	 18 (%) 23 (%)	 19 (%) 22 (%)	0.824
Age* (year)	40.24±14.07	39.64±12.53	0.835
Duration of psoriasis, year	9±11	-	
BMI* (kg/m^2)	25.32±5.11	24.69±2.85	0.616
Arthritis (n)	26 (negative)63.4% 15(positive)36.6%	-	
Nail involvement (n)	24(negative)58.5% 17(positive)41.5%	-	
PASI*	11.96±7.45		
FBG (mg/dl)	94±18	92±14	0.055
Creatinine* (mg/dl)	0.74±0.21	0.74±0.18	0.806
ALT (U/L)	20±9	19±15	0.138
AST (U/L)	19±14	19±10	0.791
Total cholesterol* (mg/dl)	188.15±34.32	189.12±40.98	0.745
Triglyceride (mg/dl)	119±94	101.5±70	0.120
LDL-C *(mg/dl)	115.29±25.10	113.56±33.21	0.606
HDL-C (mg/dl)	43±22	53.5±18	0.103
hs-CRP (mg/L)	1.64±2	1.06±1	0.117

Data expressed as median (±IQR) and *mean (±SD); Psoriasis area and severity index (PASI); Body mass index (BMI: body weight (kg)/height (cm)2; Fasting blood glucose (FBG); Alanine aminotransferase (ALT); Aspartate Aminotransferase (AST); High sensitive c-reactive protein (h-CRP); High-density lipoprotein cholesterol (HDL-C); Low-density lipoprotein cholesterol (LDL-C); Total cholesterol (TC); Triglyceride (TG); The fasting blood glucose (FBG)

Table 2 GDF-15, TNF alpha and metabolic characteristics of the psoriasis vulgaris and healthy controls

	Psoriasis vulgaris	Healthy controls	p
GDF-15 (pg/ml)	212.21±204.48	111.10±124.65	**<0.001**
TNF-α (pg/ml)	44.09±62.08	25.49±33.96	**0.015**
WC (cm)*	96.07±13.51	87.07±6.55	**<0.001**
HC (cm)*	104.85±9.04	96.71±7.55	**<0.001**
Insulin(uIU/ml)	19.21±31.60	18.62±24.65	0.871
SBP (mm-Hg)	120±20	110±19	0.061
DBP (mm-Hg)	80±10	70±18	0.074
HOMA-IR	4.23±7.33	3.61±3.5	0.379

Data expressed as median (±IQR) and *mean (±SD); Growth differantiation factor-15 (GDF-15); Tumor necrosis factor alpha (TNF-α); Homeostasis Model Assessment of insulin resistance (HOMA-IR); Waist circumference (WC), Hip circumference (HC); Systolic blood pressure (SBP) and Diastolic blood pressure (DBP).

Table 3 Correlation coefficients between GDF-15, TNF-α and other variables

	TNF-α	HOMA-IR	PASI	hs-CRP	Nail involvement	BMI	Disease duration	Arthritis
GDF-15	**r=0.455 p=0.04**	r=0.270 p=0.09	r=-0.10 p=0.951	r=-0.117 p=0.951	r=0.197 p=0.218	r=-0.046 p=0.777	r=0.063 p=0.696	0.64 0.690
TNF-α		-0.177 0.288	0.106 0.520	0.178 0.278	0.005 0.978	0.103 0.533	0.028 0.867	0.095 0.565
HOMA-IR			0.283 0.078	0.140 0.388	-0.190 0.240	0.128 0.431	0.220 0.172	-0.005 0.978
PASI				0.340 0.030	0.124 0.442	0.025 0.876	0.283 0.073	0.231 0.146
hs-CRP					**0.318 0.043**	**0.398 0.010**	0.05 0.757	0.036 0.821
Nail involvement						0.184 0.249	0.076 0.639	0.183 0.252
BMI							0.104 0.517	0.066 0.680
Disease Duration								0.024 0.884

Waist and hip circumferences were significantly higher in the patient group compared to healthy controls (p<0.001). There was no significant difference between the groups in terms of serum insulin level, systolic and diastolic blood pressures, and HOMA-IR values (Table 2). In correlation analysis; A positive correlation was found between GDF-15 and TNF-α (r=0.455, p=0.04) (Figure 3). In addition, a positive correlation was found between hs-CRP and nail involvement and BMI (r=0318, p=0.043; r=0.398, p=0.010, respectively) (Table 3).

Discussion

In this study, serum GDF-15 and TNF-α levels were found to be significantly higher in psoriasis vulgaris patients, and a positive correlation was also shown between GDF-15 and TNF-α levels, a member of the TGF beta superfamily that plays an important role in cell growth and differentiation and regulation of apoptosis, is a cytokine that emerges in response to stress and plays a role in inflammation (10). It is thought that GDF-15 is overexpressed in melanoma cells and has a role in tumor invasion (11). In addition, it has been detected in high concentrations in acute and chronic inflammation, solid cancers, kidney diseases, hematopoietic diseases, metabolic syndrome, diabetes mellitus and cardiovascular diseases and has been seen as a new inflammatory marker (12-18). Similarly, the relationship between serum GDF-15 level and disease severity is known in other inflammatory diseases such as rheumatoid arthritis, scleroderma, cancer, diabetes and coronary artery disease (12, 19, 20). In a study by Sarıyıldız et al. in Behçet's disease, it was reported that GDF-15 was associated with inflammatory response, especially joint involvement and CRP levels (21).

Although the mechanism of action of GDF-15 has not been clarified, it is known that it has a role in acute and chronic tissue damage, autocrine, anti-inflammatory and cell repair mechanisms (10, 22). Various inflammatory cytokines such as TNF-α, IL-6, IL-23, IL-22, IL-17 play a role in the development of psoriasis, and even today, treatment options targeting some of these cytokines are used. TNF-α acts as a cytokine that plays an important role in the induction of keratinocyte proliferation in the initiation of the inflammatory response in etiopathogenesis through various growth agents and cytokines. Studies have shown that TNF-α is high in patients with psoriasis and this is correlated with disease severity (23, 24). It has also been reported that the expression of GDF-15 increases by the proinflammatory cytokines such as IL-6 and TNF-α and oxidative stress, hypoxia (10, 22). This suggests that GDF-15 may have a role in the development of psoriasis.

In a study conducted by Taşolar et al. in psoriasis patients, the relationship of GDF-15 with inflammation and disease severity in psoriasis was evaluated and it was shown that GDF-15 was correlated with PASI score and TNF-α (13). In another study by Akbari et al in psoriasis vulgaris, GDF-15 serum level and GDF-15 gene expression in peripheral blood were evaluated, and it was found to be significantly higher compared to the control group. It has also been reported that GDF-15 is associated with the PASI score (6). In our study, GDF-15 was not found to be associated with PASI score, but a positive correlation was found with TNF-α, similar to the study of Taşolar et al. This suggests that GDF-15 may play a role in a pathway related to TNF-α level, which plays a role in the etiopathogenesis process in the initial stage of the disease.

In recent years, it has been known that psoriasis is no longer limited to the skin, but is associated with cardiovascular diseases, metabolic syndrome, and obesity (25). In studies, GDF-15 was detected in high concentrations in metabolic syndrome, diabetes mellitus and cardiovascular diseases, which are comorbidities accompanying psoriasis, and it was evaluated as a new inflammatory marker and also seen as a treatment target (6, 12, 14-18). Unlike the two studies conducted by Taşolar and Akbari in which GDF-15 was evaluated in psoriasis in the literature, metabolic parameters were also evaluated in psoriasis patients in our study. No correlation was found between GDF-15 and metabolic parameters. This situation supports that GDF-15 may have a role in the inflammatory steps in the formation of the disease rather than the inflammation that causes more comorbid conditions. In addition, GDF-15, which plays a role in the pathogenesis of insulin resistance and cardiovascular diseases, was not associated with insulin and HOMA-IR levels in this study. This may be due to the lack of difference between the patient and control groups in terms of HOMA-IR value and the low number of cases.

It has been reported that TNF-α increases CRP level in psoriasis patients through IL-6. However, there are variable results in the literature investigating the relationship between hs-CRP and disease severity in psoriasis. In the study of Niknezhad et al., hs-CRP was found to be high in psoriasis patients and this was also found to be associated with subclinical atherosclerosis (26). In our study, it was observed that hs-CRP level was positively correlated with especially PASI score and nail involvement. This suggests that hs-CRP may be associated with comorbidities and clinical findings that may develop related to psoriatic systemic inflammation rather than inflammation in the etiopathogenesis.

The limitations of this study are that it was not performed in larger numbers of patients with and without metabolic syndrome and these markers could not be studied in tissue with simultaneous lesions.

In conclusion, in this study, serum GDF-15 levels were found to be high in patients, and this was especially associated with TNF-α. This situation particularly supports that GDF-15 may be associated with TNF-α, which plays an important role in the etiopathogenesis of the disease and is the treatment target, in common inflammatory mechanisms. We think that it should be investigated in future studies involving larger numbers of cases.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Ethical Approval
The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Suleyman Demirel University, Faculty of Medicine Ethical Committee on October 28, 2019 (number: 294).

Consent to Participate and Publish
Written informed consent to participate and publish was obtained from all individual participants included in the study.

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Availability of Data and Materials
Data are available on request due to privacy or other restrictions.

Authors Contributions
SK: Conceptualization; Methodology; Funding acquisition; Writing-original draft.

FBŞ: Investigation; Data curation

HHAÇ: Investigation; Resources; Writing-original draft

İE: Supervision; Writing-review & editing
MY: Supervision; Writing-review & editing

Editorial
Although SK, one of the authors of the article, is

editorial board member of the journal, she has not taken part in any stage of the publication processes of this article.

References

1. Ergun T. Etiopathogenesis of Psoriasis. Turkderm 2008; 42 Suppl 2: 18-22.
2. Rendon A, Schäkel K. Psoriasis Pathogenesis and Treatment. Int J Mol Sci. 2019 23;20(6):1475.
3. Takahashi H, Iızuka H. Psoriasis and metabolic syndrome. Journal of Dermatology 2012;39:212-8.
4. Yalcin MM, Altinova AE, Akturk M, Gulbahar O, Arslan E, Sendoğan DO et al. GDF-15 and Hepcidin Levels in Nonanemic Patients with Impaired Glucose Tolerance. J Diabetes Res. 2016;2016:1240843.
5. Adela R, Banerjee SK. GDF-15 as a Target and Biomarker for Diabetes and Cardiovascular Diseases: A Translational Prospective. J Diabetes Res. 2015; 2015: 490842.
6. Akbari H, Talaee R, Zaker ZF, Nikoueinejad H. Investigating the Correlation between Growth Differentiation Factor 15 Serum Level and Its Gene Expression with Psoriasis and Its Severity. Iran J Allergy Asthma Immunol. 2021;20(5):593-599.
7. Gülekon A, Adışen E. Psoriasis and Co-morbidities. Turkderm 2008;42:2:23-5.
8. Ku SH, Kwon WJ, Cho EB, Park EJ, Kim KH, Kim KJ. The Association between Psoriasis Area and Severity Index and Cardiovascular Risk Factor in Korean Psoriasis Patients. Ann Dermatol. 2016; 28: 360-3.
9. Shashaj B, Luciano R, Contoli B, Morino GS, Spreghini MR, Rustico C et al. Reference ranges of HOMA-IR in normal-weight and obese young Caucasians. Acta Diabetol. 2016;53(2):251-60.
10. Desmedt S , Desmedt V , Leen De Vos LD, Delanghe JR, Reinhart Speeckaert R et al. Growth differentiation factor 15: A novel biomarker with high clinical potential. Crit Rev Clin Lab Sci.2019;56(5):333-350.
11. Ünal B, Alan S, Başsorgun Cİ, Karakaş AA, Elpek GÖ, Çiftçioğlu MA. The divergent roles of growth differentiation factor-15 (GDF-15) in benign and malignant skin pathologies. Arch Dermatol Res. 2015;307(7):551-7.
12. Tanrıkulu O, Sarıyıldız ME, Batmaz İ, Yazmalar L, Polat N, Kaplan İ et al. Serum GDF-15 level in rheumatoid arthritis: relationship with disease activity and subclinical atherosclerosis. Acta Reumatol Port. 2017;42(1):66-72.
13. Taşolar MK, Erfan G, Raimoğlu O, Albayrak H, Yanık ME. Role of GDF-15 as an inflammatory marker in patients with psoriasis vulgaris. Turkderm 2021;55:184-8.
14. Bao X, Borné Y, Muhammad IF, Nilsson J, Lind L,Malender O et al. Growth differentiation factor 15 is positively associated with incidence of diabetes mellitus: the Malmö Diet and Cancer-Cardiovascular Cohort. Diabetologia. 2019;62(1):78-86.
15. Pavo N, Wurm R, Neuhold S, Adlbrecht C, Vila G, Strunk G et al. GDF-15 Is Associated with Cancer Incidence in Patients with Type 2 Diabetes. Clin Chem. 2016;62(12):1612-1620.
16. Adela R, Banerjee SK. GDF-15 as a Target and Biomarker for Diabetes and Cardiovascular Diseases: A Translational Prospective. J Diabetes Res. 2015;2015:490842.
17. Echouffo-Tcheugui JB, Daya N, Matsushita K, Wang D, Ndumele CE, Rifai MA et al. Growth Differentiation Factor (GDF)-15 and Cardiometabolic Outcomes among Older Adults: The Atherosclerosis Risk in Communities Study. Clin Chem. 2021;67(4):653-661.
18. Lukaszyk E, Lukaszyk M, Koc-Zorawska E, Bodzenta-Lukaszyk A, Malyszko J. GDF-15, iron, and inflammation in early chronic kidney disease among elderly patients. Int Urol Nephrol. 2016;48(6):839-44.
19. Yanaba K, Asano Y, Tada Y, Sugaya M, Kadono T, Sato S. Clinical significance of serum growth differentiation factor-15 levels in systemic sclerosis: association with disease severity. Mod Rheumatol. 2012;22(5):668-75.
20. Wang X, Chen LL, Zhang Q. Increased Serum Level of Growth Differentiation Factor 15 (GDF-15) is Associated with Coronary Artery Disease. Cardiovasc Ther. 2016;34(3):138-43.
21. Sarıyıldız MA, Yazmalar L, Batmaz İ, Alpaycı M, Burkan YK, Sula B et al. Serum GDF-15 level in Behçet's disease: relationships between disease activity and clinical parameters Int J Dermatol . 2016;55(11):1289-1294.
22. Corre J, Hébraud H, Bourin P. Concise Review: Growth Differentiation Factor 15 in Pathology: A Clinical Role? Stem Cells Transl Med. 2013; 2(12): 946–952.
23. Kyriakou A , Patsatsi A, Vyzantiadis TA, Sotiriadis D. Serum Levels of TNF-α, IL-12/23p40, and IL-17 in Plaque Psoriasis and Their Correlation with Disease Severity. J Immunol Res. 2014; 2014: 467541.
24. Sereflican B, Goksugur N, Bugdayci G, Polat M, Parlak HA. Serum Visfatin, Adiponectin, and Tumor Necrosis Factor Alpha (TNF-α) Levels in Patients with Psoriasis and their Correlation with Disease Severity.Acta Dermatovenerol Croat. 2016;24(1):13-9.
25. Kalkan G. Comorbidities in psoriasis: The recognition of psoriasis as a systemic disease and current management. Turkderm-Turk Arch Dermatol Venereology 2017;51:71-7.
26. Niknezhad N, Haghighatkhah HA, Zargari O, Ghalamkarpour F, Younespour S, Niknejad N et al. High-sensitivity C-reactive protein as a biomarker in detecting subclinical atherosclerosis in psoriasis. Dermatol Ther. 2020;33(4):e13628.