ORIGINAL ARTICLE
Iran J Allergy Asthma Immunol
October 2021; 20(5):593-599.
Doi: 10.18502/ijaai.v20i5.7409

Investigating the Correlation between Growth Differentiation Factor 15 Serum Level and Its Gene Expression with Psoriasis and Its Severity

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Received: 21 December 2020; Received in revised form: 1 March 2021; Accepted: 15 March 2021

ABSTRACT

Psoriasis is a chronic inflammatory dermatitis characterized by an inflammatory epidermal hyperproliferation. Growth differentiation factor-15 (GDF-15), a member of the transforming growth factor-β family, has immune modulatory roles in autoimmune condition of Psoriasis. This study aimed to evaluate the relationship between GDF-15 serum levels as well as gene expression with psoriasis and its severity.

This case-control study was performed on 45 patients with psoriasis Vulgaris and 45 healthy individuals. The severity of the disease was determined based on the psoriasis area and severity index (PASI score). Serum levels of GDF-15 were measured by enzyme-linked immunosorbent assay (ELISA) and its gene expression in peripheral blood mononuclear cells was quantified by real-time polymerase chain reaction (RT-PCR).

The mean serum levels of GDF-15 in patients and controls were 1.98±1.57 ng/mL and 0.93±0.48 ng/mL, respectively. GDF-15 gene expression was measured as 9.7±6.6% in the patient group and 7.6±2.5% in the healthy group. The mean of GDF-15 serum levels in mild, moderate, and severe cases of psoriasis were 0.45±0.35, 2.27±0.7, and 3.5±1.6 ng/mL, respectively, indicating that elevated serum levels of GDF-15 correlate significantly with disease severity. The mean of GDF-15 gene expression in the mild, moderate, and severe forms of psoriasis were 5.25±3.2, 7.6±2.8, and 17.8±5.7, respectively which indicate a significant relationship between GDF-15 gene expression and psoriasis severity.

Based on this study, in psoriatic patients, GDF-15 serum levels and gene expression are significantly higher than those in healthy controls. Such values were correlated with disease activity, especially in severe cases. Therefore, GDF-15 may be used as a prognostic marker of psoriasis.

Keywords: Growth differentiation factor 15; Psoriasis

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INTRODUCTION

Psoriasis Vulgaris is one of the most common chronic skin diseases that present with erythematous scaly papules and plaques characterized by excessive proliferation and impaired keratinocyte development.[1] According to a 2020 systematic analysis study, in 2017, an estimated 29.5 million adults had psoriasis worldwide.[2] Although psoriasis is considered a skin disease, other chronic diseases such as psoriatic arthritis, metabolic syndrome, and cardiovascular diseases develop simultaneously in some patients.[3] Such complicated features of the disease necessitate a better understanding of its exact inflammatory pathways. One way to show such inflammatory nature is indicated by the high presence of systemic as well as cutaneous proinflammatory cytokines such as interleukin (IL)-23, IL-22, IL-20, IL-19, IL-17, IL-8, IL-12, IL-6, IL-2, IL-24, interferon-gamma (IFN-γ), and tumor necrosis factor-alpha (TNF-α).[4] In addition, this disease has been introduced as an autoimmune disease caused by T lymphocytes.[5]

The transforming growth factor-beta (TGF-β) superfamily consists of molecules that regulate a variety of cellular processes, including growth, differentiation, and carcinogenesis. Growth differentiation factor 15 or macrophage inhibitory cytokine 1 (GDF-15/MIC-1) is a distant member of such family.[6] GDF-15 is a stress response cytokine expressed in large amounts in cardiomyocytes, adipocytes, endothelial cells, macrophages, and vascular smooth muscle cells under normal and pathological conditions[7] such as apoptotic pathways in damaged body tissues.[8] It has also some metabolic effects concerning body weight and food intake.[9] Moreover, it also shows some tolerating roles in both bacterial and viral infections which survive the host in such infections.[10]

GDF-15 levels may have some useful clinical applications in several inflammatory and malignant diseases such as colon, pancreatic, prostate, ovarian, and thyroid cancers, cardiovascular events, atherosclerosis, pulmonary embolism, and rheumatoid arthritis.[11] Also, GDF-15 can be used as a therapeutic target to control inflammatory processes due to its inhibitory role in leukocytes function[12,13] This study aimed to evaluate serum GDF-15 levels and their gene expression in peripheral blood mononuclear cells of psoriatic patients. Demonstrating a significant and direct relationship between serum levels as well as gene expression of such factor with psoriasis and its severity, we aimed to verify its role in the immune pathogenesis of psoriasis. Such a finding may be effective in treating the disease through GDF-15, especially in the early stages of the disease. This is especially important when we note that there are currently no effective treatments for psoriasis.

MATERIALS AND METHODS

This case-control study was performed on 45 patients with psoriasis Vulgaris referred to the dermatology clinic of Shahid Beheshti Hospital of Kashan, the center of Iran, as the study group and 45 healthy individuals as a control group. All the patients were in the remission phase. Smoking, corticosteroid therapy, and any other autoimmunity, as well as an infectious or inflammatory disease, were considered as exclusion criteria. A dermatologist thoroughly and carefully examined each undergone patient for all possible clinical signs. Forty seven healthy volunteers without a history of psoriasis and other autoimmune as well as inflammatory diseases were included as the healthy control group. The study protocol was conformed to the ethical guidelines of the 1975 Helsinki Declaration and was approved by the ethical local committee (No IR.KAUMS.REC.96132). Written informed consent was obtained from all participants. A questionnaire containing patient information was completed.

Method of psoriasis area and severity index (PASI) score was used to classify psoriatic patients to different severities. PASI score is based on the lesion's severity and affected area extension and includes a scale between 0 (no disease) and 72 (maximum disease). It was considered as mild from 0 to 9.9, moderate from 10 to 19.9, and severe more than 20.[13]

Experiments

Three milliliters venous blood sample was obtained from all participants. Each blood sample was centrifuged immediately and the serum was stored at −80°C until analysis. The serum GDF-15 levels were measured by enzyme-linked immunosorbent assay (ELISA) method using GDF-15 Human kit (Invitrogen) (with an analytical sensitivity of 2 pg/mL and assay range of 1.1-800 pg/mL). Expression of the GDF-15 gene was measured by real-time polymerase chain

reaction (RT-PCR) after isolation of peripheral blood mononuclear cells (PBMCs) from 2 mL of EDTA-anticoagulated blood by Ficoll-Hypaque (Lymphodex, Inno-Train, Germany) density gradient centrifugation. Total RNA was extracted from PBMC (High Pure RNA Isolation Kit, Cat No: 11828665001, Roche Applied Science), cDNA synthesized from the extracted RNA (Transcriptor First Strand cDNA Synthesis Kit, Cat No: 04897030001, Roche Applied Science). The amount of GDF-15 gene expression was measured through Taqman primer-probe Comparative cycle threshold (CT) method (ABI 7300 RT-PCR system) under the conditions of the initial cycle at 95℃ for 10 min, followed by 40 cycles at 95℃ for 15 sec and 60℃ for 1 min. The below primers for GDF-15 were used:

GDF-15, forward 5'-GTT AGC CAA AGA CTG CCA CTG-3', reverse 5'-CCT TGA GCC CAT TCC ACA-3.[14] β-actin housekeeping gene was used as endogenous control with below primers:

β-actin, forward 5'-ACT TAG TTG CGT TAC ACC CTT TCT-3' and reverse 5'-GAC TGC TGT CAC CTT CAC CGT-3'. After confirming the efficacy of RT-PCR about the gene and its internal control, the gene expression in patients was compared with controls.

Statistical Analysis

SPSS software version 16.0 (SPSS, Inc, USA) was used for statistical analysis. The normality of the data was calculated; using the Shapiro Wilk test. A Chi-square test was used to examine the association between the groups and qualitative variables. Independent T-test and ANOVA were used to compare the quantitative variables between two groups. Error bars were demonstrated by mean and 95% confidence interval. A multiple Linear regression model was used to evaluate the effect of psoriasis on GDF-15 serum level as well as its gene expression by omitting the effect of confounding variables. Adjusted R square was considered as a criterion for the goodness of fittest.

RESULTS

Demographic, clinical, and laboratory characteristics of all participants are shown in table 1. There was a significant increase in the psoriatic patients according to positive family history of psoriasis (p=0.02). Mean serum level of GDF-15 in the patients, and healthy controls were 1.98 and 0.93 pg/mL respectively (p<0.001); and the mean of the gene expression level of *GDF-15* in the patients and healthy controls were 9.7 and 7.6, respectively (p=0.05) (Table 1).

Table 1. Demographic, clinical, and laboratory characteristics of all participants

Characteristics		Case	Control	*p*
Sex	male	30 (66.7%)	28 (62.2 %)	0.66[1]
	female	15 (33.3%)	17 (37.8 %)	
Family history	positive	11 (24.4%)	3 (6.7 %)	**0.02[1]**
	negative	34 (75.6%)	42 (93.3 %)	
Disease duration (month)($\bar{X} \pm SD$)		6.8±11.38	-	-
Age (year) ($\bar{X} \pm SD$)		34.2±12.3	35 ± 9.5	0.71[2]
GDF-15 serum level (ng/mL) ($\bar{X} \pm SD$)		1.98±0.57	0.93 ± 0.48	< 0.001[2]
GDF-15 gene expression (%) ($\bar{X} \pm SD$)		9.7 ±6.6	7.6 ± 2.5	0.05[2]
GDF-15 serum level (ng/mL) in different PASI scores	Mild (to 9.9)	0.45±0.35	-	<0.001[3]
	Moderate (10-19.9)	2.27 ±0.7		
	Sever (20-72)	3.5 ±1.6		
GDF-15 gene expression (%) in different PASI scores	Mild (to 9.9)	5.25 ±3.2	-	<0.001[3]
	Moderate (10-19.9)	7.6 ±2.8		
	Sever (20-72)	17.8±5.7		

Growth differentiation factor-15 (GDF-15); psoriasis area and severity index score (PASI score)

1: Chi-square test 2: Independent T-test 3: ANOVA test

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Mean serum levels of GDF-15 in patients with and without a positive family history of psoriasis were 3.18 and 1.59 pg/mL, respectively (p=0.003). Mean values of *GDF-15* gene expression in patients with and without a positive family history of psoriasis were 12.1 and 8.94 pg/mL, respectively (p=0.169). There was not any significant correlation between GDF-15 and its gene expression with a positive family history in healthy controls (p>0.33). Mean serum levels of GDF-15 in patients suffering less and more than one year from psoriasis were 1.06 and 3.25 pg/mL, respectively (p<0.001).

Mean values of GDF-15 gene expression in patients suffering less and more than one year from psoriasis were 7.58 and 12.63 pg/mL, respectively (p=0.009). There was a significant correlation between GDF-15 as well as its gene expression with the duration of the disease (p<0.01).

The more severe forms of psoriasis had higher serum levels of GDF-15 (P<0.001) as well as its gene expression (p<0.001) (Table 1) (Figure 1). The linear correlation coefficient between serum and gene expression levels of GDF-15 and PASI score was equal to 0.803 (p<0.001) and 0.848 (p<0.001), respectively (data not shown).

Multiple linear regression models showed that even in the presence of other variables including sex, age, and positive family history any increase in serum levels of GDF-15 as well as its gene expression is positively related to the severity of psoriasis (p<0.001) (Table 2). Results of adjusted R square analysis show that such regression model could clearly explain the effect of severity of the disease on the serum levels of GDF-15 (Adjusted R^2= 0.667) and its gene expression (Adjusted R^2=0.709).

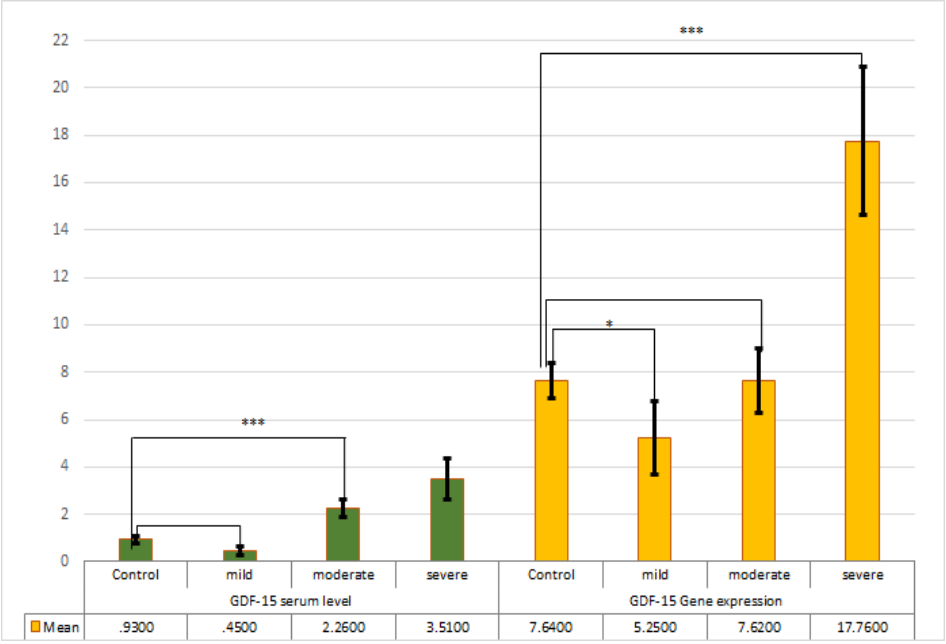

Figure 1. Mean and 95% confidence interval of growth differentiation factor-15 (GDF-15) serum level and its gene expression. The graph shows that serum and gene expression levels of GDF-15 in psoriatic patients are significantly more than those in healthy controls. More severe forms of the disease showed more such levels *p<0.05, ***p<0.001.

Table 2. Multiple linear regression coefficients of the effect of the different factors on serum Growth differentiation factor-15 (GDF-15) levels and its gene expression

GDF-15	MODEL	Unstandardized Coefficients		t	Sig.	Adjusted R Square
		B	Std. Error			
serum levels	Constant	-0.315	0.407	-0.773	0.444	0.667
	PASI score	0.112	0.016	6.983	<0.001	
	Age	0.014	0.012	1.101	0.278	
	Sex	0.269	0.297	0.908	0.369	
	Family history	0.660	0.335	1.969	0.056	
gene expression	Constant	1.018	1.589	0.641	0.525	0.709
	PASI score	0.557	0.063	8.882	<0.001	
	Age	0.044	0.048	0.908	0.369	
	Sex	-1.041	1.158	-0.899	0.374	
	Family history	-1.273	1.309	-0.973	0.336	

DISCUSSION

According to our knowledge, this study is the first one investigating the changes of GDF-15 serum levels along with its gene expression in PBMCs as indicators of diagnosis as well as severity estimation of psoriasis. In our study, we showed a significant relationship between serum levels as well as gene expression of GDF-15 and psoriasis, both of which correlated with disease severity. Such correlation between the serum levels of GDF-15 and disease severity has also been shown in other inflammatory pathologies such as rheumatoid arthritis,[15-18] scleroderma,[19,20] cancer,[21,22] diabetes and coronary artery disease,[23] Idiopathic pulmonary fibrosis,[24] Idiopathic inflammatory myopathies,[25] and spondyloarthropathy;[26] in the latter one as a biomarker of bone erosion. Although one study did not find a significant increase of GDF-15 in Behcet's disease, it showed a significant positive correlation between serum levels of GDF-15 and peripheral arthritis, erythema nodosum as well as arthralgia, suggesting that this factor may play a role in the progression of such disease and its pathology.[27]

In the case of GDF-15 gene expression, a study showed that dysregulated genetic alterations in the expression of GDF-15 in keratinocytes of the psoriatic patients have some roles in the pathogenicity of the disease. This study suggested that IRS-2 and GDF-15 can be classified as candidate genes for psoriasis gene therapy.[28] The other study showed that GDF-15 gene expression could be used as a reliable sensitive biomarker for prediction of the acute coronary syndrome.[29] Such studies are in line with our investigation which showed a positive correlation between GDF-15 and psoriasis severity.

Elevated levels of GDF-15 may have both protective and pathogenic roles in different diseases. For example, reduced abundance of GDF-15 in post mortem islets of mice with non-obese diabetes corroborated that elevated GDF-15 activity in pancreatic beta cells may protect such cells under inflammatory conditions of the disease.[30] Several other reports have also described GDF-15 as a regulator of the inflammatory responses.[31,32] Paradoxically, a study on T-cell-mediated autoimmune disease of severe aplastic anemia indicated that GDF-15 might play an important role in ineffective erythrocytopoiesis and iron metabolism.[33] Another study could not conclude a potential inhibitory role for GDF-15 in the lungs of mice with idiopathic pulmonary fibrosis.[24] Genetic and environmental stats may define such positive and negative evolutional effects of GDF-15. For instance, in the case of cancers, under physiological and pathophysiological conditions, GDF-15 inhibits and accelerates tumor growth, respectively.[34] In our study, we may consider two different hypotheses. The first hypothesis states that, regarding immunomodulatory effects of GDF-15, an increase of its serum, as well as gene expression levels in severe forms of

psoriasis, may delay the progression of the psoriatic process to more severe types. Strengthening this hypothesis, we should consider that GDF-15 acts as a β2 integrin-antagonist which traps leukocytes on the endothelium preventing them from migrating to the inflammation area.[12] Regarding GDF-15 pathogenic roles, the second hypothesis expresses that such an increase may deteriorate the inflammatory condition of psoriasis. Further studies should more clarify such ambiguous aspects of GDF-15 in psoriasis.

Omitting the effects of different confounding factors of sex, age, and positive family history, we confirmed that the serum levels, as well as gene expression of GDF-15, are correlated with psoriasis severity. Such a finding may introduce GDF-15 as a marker of psoriasis severity. This is in line with some above-mentioned studies emphasizing the prognostic value of GDF-15 in psoriasis. In this regard, GDF-15 may be used as a target for some therapies to reduce disease severity.

The limitation of our study was that firstly, we did not monitor the changes of DGF-15 longitudinally. This limitation allowed just a cross-sectional analysis of GDF-15 profiles. Secondly, we did not assay the GDF-15 changes locally in the affected area of the skin. Such measurement could represent more information about the pathologic roles of GDF-15 in psoriasis. Thirdly, functional assays which provide further information on molecular mechanisms of inflammatory and/or anti-inflammatory effects of DGF-15 were not performed.

According to our results, serum levels and expression of the GDF-15 gene are higher in psoriasis patients which are correlated to the disease severity independent of other factors. It may be possible that such measurements predict the progression of psoriasis in the early and mild stages of the disease.

CONFLICT OF INTEREST

There is no conflict of interest.

ACKNOWLEDGEMENTS

This study was originated from the studies related to research supported by the Deputy of Research, Kashan University of Medical Sciences (KAUMS), Grant No 3472.

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