Original Article

Growth Differentiation Factor-15: One of the Missing Links between Psoriasis and Metabolic Syndrome

Essam M. Akl[1], Nehad A. Fouad[2], Maram S. Mahmoud[3], Karem T. Khalil[1]

Departments of [1]Dermatology, Venereology and Andrology, [2]Medical Microbiology and Immunology, [3]Faculty of Medicine, Benha University, Benha, Al-Qalyubia Governorate, Egypt

Abstract

Background: Psoriasis is a chronic inflammatory condition of the skin that can be related to a variety of other conditions, including cardiovascular disease and metabolic syndrome. Growth differentiation factor-15 (GDF-15) is a cytokine that reacts to cellular stress. GDF-15 serum levels may have clinical uses in a variety of inflammatory and cardiovascular conditions. **Objectives:** To determine the levels of GDF-15 in the serum of patients with generalized plaque psoriasis (GPP) and its correlation with the metabolic syndrome. **Patients and Methods:** This case-control study included 50 patients with GPP and 50 age- and sex-matched healthy volunteers as controls. A general examination was performed, with a particular emphasis on measurements of body mass index, circumference of the waist, and blood pressure. Psoriasis severity was assessed using the Psoriasis Area and Severity Index (PASI) score. In addition, laboratory tests, including fasting blood sugar, lipid profile, and serum GDF-15 level measurement, were made. **Results:** Patients had significantly higher median GDF-15 levels compared to controls ($P < 0.001$). GDF-15 showed a substantial correlation with both disease duration and PASI score ($P < 0.001$ for each). GDF-15 levels were considerably greater in participants with metabolic syndrome compared with those without ($P = 0.01$). **Limitation:** The relatively small sample size could be a disadvantage and drawback of the study. **Conclusion:** Serum GDF-15 levels are linked to the severity of psoriasis and the associated metabolic disorders.

Keywords: *Growth differentiation factor-15, metabolic syndrome, psoriasis*

Introduction

Psoriasis is a persistent, inflammatory skin disease that affects people who are genetically prone to it. It affects approximately 2% of the population, with over 50 percent of cases occurring during the first thirty years of life.[1] It is closely associated with cardiovascular disease, diabetes, and metabolic disorders such as overweight, high blood pressure, and dyslipidemia.[2]

Growth differentiation factor-15 (GDF-15), a member of the transforming growth factor β family, has been linked to cardiovascular, metabolic, and inflammatory illnesses. GDF-15 is found throughout the majority of tissues, including endothelial cells and fat cells.[3,4] Therefore, this study aimed to measure the serum level of GDF-15 and evaluate its link to metabolic syndrome (MetS) in psoriatic patients compared with healthy controls.

Patients and Methods

The time frame for this case-control study was March 2022-August 2023. The outpatient clinic at Benha University Hospitals' Department of Dermatology, Venereology, and Andrology was used to enroll 100 participants.

The study was done with authorization from the Benha Faculty of Medicine's ethical committee for human subjects research (Ms.26.11.2021). All participants provided signed and informed permission.

Participants were split up into two groups: patient group ($n = 50$) and age- and sex-matched control group ($n = 50$).

Patients who had been diagnosed with generalized plaque psoriasis for more than six months and had a Psoriasis Area and Severity Index (PASI) score of at least eight were included in the study.

Participants were not allowed to take part in the study if they had unstable psoriasis (pustular or erythrodermic psoriasis), psoriatic arthritis, systemic or topical

How to cite this article: Akl EM, Fouad NA, Mahmoud MS, Khalil KT. Growth differentiation factor-15: One of the missing links between psoriasis and metabolic syndrome. Indian Dermatol Online J 2025;16:397-401.

Received: 05-Jun-2024. **Revised:** 27-Sep-2024. **Accepted:** 28-Oct-2024. **Published:** 01-Apr-2025.

Address for correspondence:
Dr. Karem T. Khalil, Department of Dermatology, Venereology and Andrology, Faculty of Medicine, Benha University, Benha, Postal Code - 13511, Egypt.
E-mail: Karem.khalil@fmed.bu.edu.eg

Access this article online

Website: https://journals.lww.com/idoj

DOI: 10.4103/idoj.idoj_546_24

Quick Response Code:

medication for psoriasis in the month prior to the study, pregnant or nursing women.

A thorough medical history and a general examination, including blood pressure readings (both diastolic (DBP) and systolic (SBP)), were performed on each participant. The focus of anthropometric measurements was on waist circumference (WC) and body mass index (BMI), which was calculated as weight (kg) divided by height (m^2). The cutaneous examination was conducted by calculating the PASI score to determine the type, site, extent, and severity of psoriasis.

The modified National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) recommendations were used to analyze the MetS criteria. Three of the following criteria were necessary for the diagnosis: WC of 102 cm in men or 88 cm in women is the first indicator of abdominal obesity. Other indicators include serum triglycerides (TG) of 150 mg/dL, high-density lipoprotein-cholesterol (HDL) of 40 mg/dL in men or 50 mg/dL in women, fasting blood sugar (FBS) of 100 mg/dL, and blood pressure of 130/85 mmHg.[5]

Each participant had a five-milliliter venous blood sample drawn to test their FBS and lipid profile. Additionally, blood GDF-15 was measured using the commercially available specific kit (Cat #: DZE201120038, HuTai Road, Baoshan District, Shanghai, China) and the enzyme-linked immunosorbent assay (ELISA) approach.

Statistical analysis

The data were analyzed with SPSS Version 25 (IBM Inc., Chicago, IL, USA). Analytical statistics such as the Student's *t*-test and Mann–Whitney U-test were used, along with descriptive statistics such as mean, standard deviation, number, percent, median, and range. Several tests were used, including the Chi-square test, Pearson correlation coefficient test, and receiver operating characteristic (ROC) curve, with significance set at $P < 0.05$.

Results

The study groups had no significant differences in age, gender, BMI, or WC ($P > 0.05$) for each. Patients had considerably higher mean SBP and DBP versus controls ($P = 0.01$ and 0.04, respectively) [Table 1].

Patients had significantly increased mean FBS and TG levels compared to controls ($P = 0.04$ and 0.01, respectively). Patients showed considerably greater median GDF-15 levels versus controls ($P < 0.001$). There was no significant difference in cholesterol, HDL, or low density lipoprotein (LDL) levels between patients and controls ($P > 0.05$) [Table 2].

GDF-15 showed a substantial correlation with both disease duration ($P < 0.001$) and PASI score ($P < 0.001$). There was an insignificant relation between GDF-15 and the other variables, including patient age, BMI, SBP, DBP, FBS, cholesterol, TG, HDL, and LDL ($P > 0.05$ for each) [Table 3, Figures 1 and 2].

Participants with MetS had significantly greater levels of GDF-15 than those without ($P = 0.01$) [Table 4].

A ROC curve demonstrated that a GDF-15 cut-off value of 1699.7 pg/dl may predict Mets risk in psoriasis patients with 85% sensitivity and 86.7% specificity (Area under the curve (AUC): 0.90 and 95% confidence interval (CI): 0.82-0.98) [Figure 3].

Discussion

Among the various cutaneous disorders associated with MetS, psoriasis has the strongest association.[6] Psoriatic patients have a minimum of two-fold increased chance of developing MetS. Patients over 40 years of age and those with higher PASI scores are more likely to experience MetS.[7]

According to the current study, psoriatic patients had higher levels of MetS than controls. Patients with psoriasis had noticeably higher mean SBP and DBP. Comparable

Table 1: Clinical characteristics of the study groups

	Patient (*n*=50)	Control (*n*=50)	Test of significance	*P*
Age (Year) (Mean±SD)	47.1±12.5	43.2±12.6	*t*=1.3	0.2
BMI (Kg/m^2) (Mean±SD)	28.59±4.57	27.03±3.86	*t*=1.6	0.1
Waist circumference (Cm) (Mean±SD)	85.36±12.03	81.03±8.9	*t*=1.7	0.1
Sex				
Female *n* (%)	25 (50%)	30 (60%)	χ^2=0.8	0.4
Male *n* (%)	25 (50%)	20 (40%)		
SBP (mmHg) (Mean±SD)	127.60±16.23	118.00±14.95	*t*=2.6	0.01*
DBP (mmHg) (Mean±SD)	81.80±7.20	78.33±6.99	*t*=2.1	0.04*
Metabolic syndrome				
Present *n* (%)	21 (42)	7 (14)	χ^2=9.7	0.001*
Absent *n* (%)	29 (58)	43 (86)		

*Significant. *t*=Independent *t*-test, χ^2=Chi-square test. SD=Standard deviation, BMI=Body mass index, SBP=Systolic blood pressure, DBP=Diastolic blood pressure

Table 2. Laboratory data of the study groups

	Mean±S.D		Test of significance	*P*
	Patient (*n*=50)	Control (*n*=50)		
FBS (mg/dl)	132.40±19.42	123.20±17.92	*t*=2.1	0.04*
Cholesterol (mg/dl)	192.50±54.29	188.00±55.68	*t*=0.4	0.4
TG (mg/dl)	143.42±63.49	114.10±34.83	*t*=2.6	0.01*
HDL (mg/dl)	38.92±5.57	40.23±4.861	*t*=1.1	0.1
LDL (mg/dl)	62.92±46.32	66.10±43.724	*t*=0.3	0.8
GDF-15(pg/dl)				
Median	1670.43	704.09	Mann-Whitney *U*=5.5	<0.001*
Range	546.41-9853.08	90.19-3963.67		

*Significant, S.D=Standard deviation, FBS=Fasting blood sugar, TG=Triglycerides, HDL=High density lipoprotein, LDL=Low density lipoprotein, GDF-15=Growth differentiation factor-15

Table 3: Correlation between GDF-15 and other variables

	r	*P*
Age	0.05	0.74
BMI	0.07	0.64
Waist circumference	0.118	0.299
SBP	0.104	0.358
DBP	0.122	0.280
FBS	0.103	0.365
Duration of psoriasis	0.53	<0.001*
PASI score	0.61	<0.001*

*Significant, BMI=Body mass index, SBP=Systolic blood pressure, DBP=Diastolic blood pressure, PASI=Psoriasis area severity index, *r*=Pearson's correlation coefficient

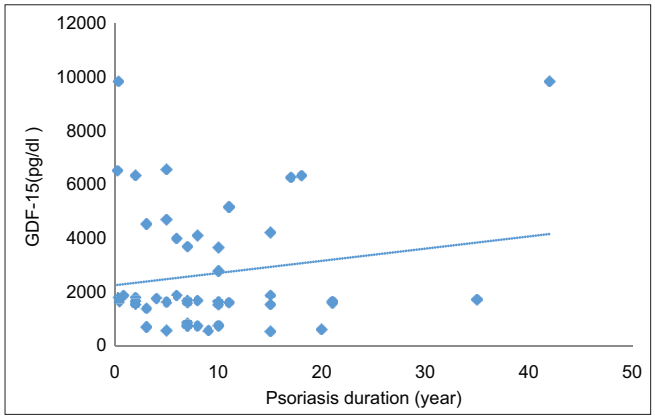

Figure 1: Correlation between growth differentiation factor-15 (GDF-15) and psoriasis duration

outcomes were also documented.[8,9] Additionally, a favorable relationship between blood pressure and PASI was shown.[10-12] However, Langan *et al.*[13] argued that there was no evident association.

Psoriasis, hypertension, and Mets have been interconnected in a number of studies, particularly due to chronic inflammation. These three conditions cause oxidative damage to nucleic acids and share inflammatory and anti-inflammatory signals.[14]

In the same context, compared to controls, the included patients had significantly higher mean FBS and TG. This is consistent with the findings of Qian *et al.*[15] who found that 685 psoriasis patients had blood glucose levels that were greater than those of the controls.

Studies on the relationship between psoriasis and dyslipidemia have shown mixed results. In certain research, psoriasis patients had noticeably greater triglyceride levels than controls, but there was no discernible change in their HDL levels.[16,17] Similarly, Gisondi *et al.*[18] showed that psoriasis patients had higher rates of hypertriglyceridemia and Mets than controls. However, there was no difference in HDL, diabetes, or hypertension levels. However, Farshchian *et al.*[19] found no difference between psoriasis patients and controls in terms of FBS, TG, cholesterol, HDL, LDL, and VLDL levels.

Blood GDF-15 levels have shown a significant association with inflammatory diseases, such as rheumatoid arthritis, scleroderma, and coronary artery disease.[20-22] By acting on nearby cells, the released GDF-15 can control inflammatory interactions in autocrine, paracrine, and endocrine ways. GDF-15 often sets off an adaptive response that protects tissue by strongly inhibiting proliferation, inflammation, and apoptosis.[23]

The current study found that patients had significantly higher median GDF-15 levels than controls. GDF-15 showed a statistically significant positive correlation with disease duration and PASI score. This is consistent with the findings of Taşolar *et al.*[24] and Akbari *et al.*[25] who discovered that the more severe forms of psoriasis had higher GDF-15 serum levels and gene expression.

Various hypotheses might be proposed for the action of GDF-15 in psoriasis. The first hypothesis proposes that, in terms of immunomodulatory protective actions, an increase in its serum and gene expression levels in severe forms of psoriasis may delay the progression of the disease to more severe forms. GDF-15 works as a β2 integrin antagonist, trapping leukocytes on the endothelium and preventing them from moving to the inflammatory region.[26] The

Table 4: Serum GDF-15 level according to the presence of metabolic syndrome

	MetS Present (*n*=28)		MetS Absent (*n*=72)		Mann-Whitney *U*	*P*
	Median	Range	Median	Range		
GDF-15 (pg/dl)	1708.6	622.6-9853.1	824.2	90.2-6570.2	2.6	0.01*

*Significant, GDF-15=Growth differentiation factor-15

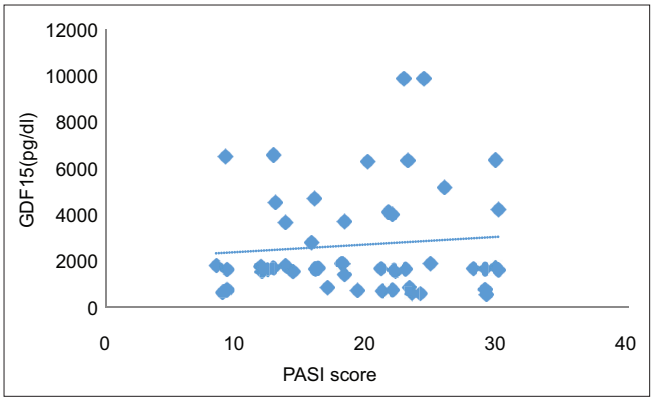

Figure 2: Correlation between growth differentiation factor-15 (GDF-15) and Psoriasis Area and Severity Index (PASI) score

second hypothesis states that such an increase may worsen the inflammatory condition of psoriasis.[25]

On the other hand, participants with MetS had considerably greater levels of GDF-15 than those without. This is congruent with Carballo-Casla *et al*.[27], who found that MetS was consistently related to greater GDF-15 levels. Shin *et al*.[28] documented the link between serum GDF-15 levels and cardiovascular risk.

Lipid disorders are a defining hallmark of MetS and a major cause of coronary artery disease. The existing study demonstrated no significant relationship between GDF-15 and lipid profile, blood sugar, or blood pressure. Similarly, a study found no correlation between GDF15 levels and LDL, triglycerides, or total cholesterol. However, the same study found that GDF15 was substantially related to lower HDL.[29] Investigations have established a link among hypertension, GDF15 expression, and circulating serum levels.[30]

Limitations

The primary drawback of the current work may be its single-centered design and small sample size. Longitudinal investigations of GDF-15 in psoriatic patients of all ages, including children and adults, are advised. Further studies into serum GDF-15 levels before and after psoriasis treatments or lifestyle and dietary modifications may provide additional advantages.

Conclusion

The results presented above suggest that in psoriatic individuals, serum GDF¬-15 may serve as a marker for the onset of Mets.

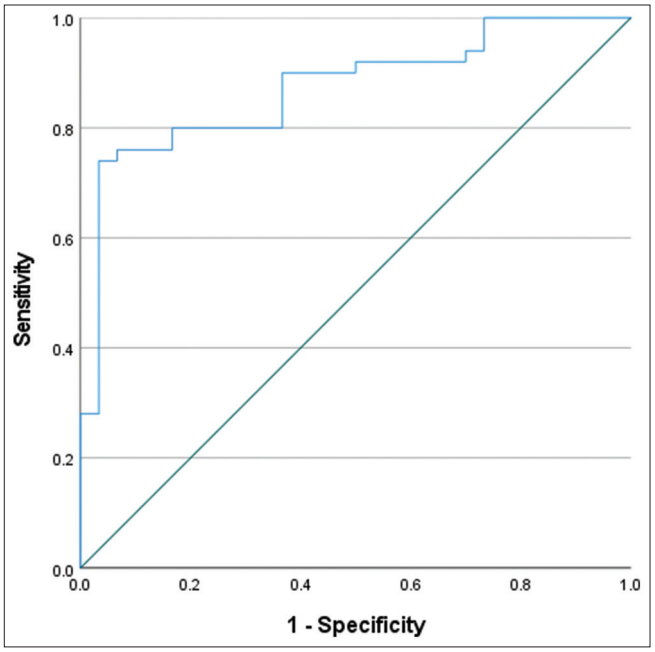

Figure 3: Receiver operating characteristic (ROC) curve analysis of growth differentiation factor-15 (GDF-15) for prediction of metabolic syndrome in psoriatic patients

Acknowledgments

We are grateful to all patients and volunteers who took part in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Kamiya K, Kishimoto M, Sugai J, Komine M, Ohtsuki M. Risk factors for the development of psoriasis. Int J Mol Sci 2019;20:4347.
2. Takeshita J, Grewal S, Langan SM, Mehta NN, Ogdie A, Van Voorhees AS, *et al*. Psoriasis and comorbid diseases: Epidemiology. J Am Acad Dermatol 2017;76:377-90.
3. Luan HH, Wang A, Hilliard BK, Carvalho F, Rosen CE, Ahasic AM, *et al*. GDF15 is an inflammation-induced central mediator of tissue tolerance. Cell 2019;178:1231-44.
4. Man L, Duan L, Cai Y, Li H, Hao BC, Chen J, *et al*. Growth differentiation factor-15 is associated with cardiovascular outcomes in patients with coronary artery disease. Cardiovasc Diabetol 2020;19:120.
5. Kaur J. Assessment and screening of the risk factors in metabolic syndrome. Med Sci 2014;2:140- 52.

6. Agarwal K, Das S. Metabolic syndrome-the underbelly of dermatology. Gulf J Dermatol Venerol 2019;26:1-10.
7. Gisondi P, Fostini AC, Fossà I, Girolomoni G, Targher G. Psoriasis and metabolic syndrome. Clin Dermatol 2018;36:21-8.
8. Armesto S, Coto-Segura P, Osuna CG, Camblor PM and Santos-Juanes J. Psoriasis and hypertension: A case-control study.J Eur Acad Dermatol Venereol 2012;26:785-8.
9. Armstrong AW, Siegel MP, Bagel J, Boh EE, Buell M, Cooper KD, *et al*. From the medical board of the national psoriasis foundation: Treatment targets for plaque psoriasis. J Am Acad Dermatol 2017;76:290-8.
10. Al-Mutairi N, Al-Farag S, Al-Mutairi A, Al-Shiltawy M. Comorbidities associated with psoriasis: An experience from the Middle East. J Dermatol 2010;37:146-55.
11. Salihbegovic EM, Hadzigrahic N, Suljagic E, Kurtalic N, Sadic S, Zejcirovic A, *et al*. Psoriasis and high blood pressure. Med Arch 2015;69:13-5.
12. Takeshita J, Wang S, Shin DB, Mehta NN, Kimmel SE, Margolis DJ, *et al*. Effect of psoriasis severity on hypertension control: A population-based study in the United Kingdom. JAMA Dermatol 2015;151:161-9.
13. Langan SM, Seminara NM, Shin DB, Troxel AB, Kimmel SE, Mehta NN, *et al*. Prevalence of metabolic syndrome in patients with psoriasis: A population-based study in the United Kingdom. J Invest Dermatol 2012;132:556-62.
14. Paschoal RS, Silva DA, Cardili RN, Souza CDS. Metabolic syndrome, C-reactive protein and cardiovascular risk in psoriasis patients: A cross-sectional study. An Bras Dermatol 2018;93:222-8.
15. Qian H, Kuang Y, Su J, Chen M, Chen X, Lv C, *et al*. Reductive effect of acitretin on blood glucose levels in Chinese patients with psoriasis. Front Med (Lausanne) 2021;8:764216.
16. Nisa N, Qazi MA. Prevalence of metabolic syndrome in patients with psoriasis. Indian J Dermatol Venereol Leprol 2010;76:662-5.
17. Madanagobalane S, Anandan S. The increased prevalence of non-alcoholic fatty liver disease in psoriatic patients: A study from South India. Australas J Dermatol 2012;53:190-7.
18. Gisondi P, Tessari G, Conti A, Piaserico S, Schianchi S, Peserico A, *et al*. Prevalence of metabolic syndrome in patients with psoriasis: A hospital-based case-control study. Br J Dermatol 2007;157:68-73.
19. Farshchian M, Zamanian A, Farshchian M, Monsef AR, Mahjub H. Serum lipid level in Iranian patients with psoriasis. J Eur Acad Dermatol Venereol 2007;21:802-5.
20. Osman T, Mustafa AS, Ibrahim B, Levent Y, Nihat P, İbrahim K, *et al*. Serum GDF-15 level in rheumatoid arthritis: Relationship with disease activity and subclinical atherosclerosis. Acta Reumatol Port 2017;42:66-72.
21. Gamal SM, Elgengehy FT, Kamal A, El Bakry SA, Shabaan E, Elgendy A, Bassyouni IH. Growth differentiation factor-15 (GDF-15) level and relation to clinical manifestations in egyptian systemic sclerosis patients: Preliminary data. Immunol Invest 2017;46:703-13.
22. Bao X, Borne Y, Muhammad IF, Nilsson J, Lind L, Melander O, *et al*. Growth differentiation factor 15 is positively associated with incidence of diabetes mellitus: The Malmo diet and cancer-cardiovascular cohort. Diabetologia 2019;62:78-86.
23. Yang L, Chang CC, Sun Z, Madsen D, Zhu H, Jorgensen SB, *et al.* GFRAL is the receptor for GDF-15 and is required for the anti-obesity effects of the ligand. Nat Med 2017;23:1158-66.
24. Taşolar MK, Erfan G, Raimoğlu O, Albayrak H, Yanık ME. Role of GDF-15 as an inflammatory marker in patients with psoriasis vulgaris. Turkderm-Turk Arch Dermatol Venereol 2021;55:184-8.
25. Akbari H, Talaee R, Zaker SF, 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;20:593-9.
26. Zarbock A, Kempf T, Wollert KC, Vestweber D. Leukocyte integrin activation and deactivation: Novel mechanisms of balancing inflammation. J Mol Med (Berl) 2012;90:353-9.
27. Carballo-Casla A, García-Esquinas E, Buño-Soto A, Struijk EA, López-García E, Rodríguez-Artalejo F, *et al*. Metabolic syndrome and growth differentiation factor 15 in older adults. Geroscience 2022;44:867-80.
28. Shin MY, Kim JM, Kang YE, Kim MK, Joung KH, Lee JH, Kim KS, *et al*. Association between growth differentiation factor 15 (GDF15) and cardiovascular risk in patients with newly diagnosed type 2 diabetes mellitus. J Korean Med Sci 2016;31:1413-18.
29. Cheung CL, Tan KCB, Au PCM, Li GHY, Cheung BMY. Evaluation of GDF15 as a therapeutic target of cardiometabolic diseases in human: A Mendelian randomization study. EBioMedicine 2019;41:85-90.
30. Asrih M, Wei S, Nguyen TT, Yi HS, Ryu D. Overview of growth differentiation factor 15 in metabolic syndrome. J Cell Mol Med 2023;27:1157-67.