Original Article

Evaluation of Serum Progranulin Levels in Patients with Psoriasis: A Case-control Study

Rıdvan Güneş, Pınar İncel Uysal[1], Başak Yalçin[2], Çiğdem Yücel[3], Ömer Kutlu[4]

Nevsehir State Hospital, Department of Dermatology and Venereology, Nevşehir, Turkey, [1]TOBB ETU Faculty of Medicine, Department of Dermatology, Ankara, Turkey, [2]Ankara Bilkent City Hospital, Department of Dermatology and Venereology, Ankara, Turkey, [3]Ankara Numune Training and Research Hospital, Department of Biochemistry, Ankara, Turkey, [4]Tokat Gaziosmanpaşa University, School of Medicine, Department of Dermatology and Venereology, Tokat, Turkey

Abstract

Objectives: T cells, keratinocytes, dendritic cells, inflammatory cytokines including tumor necrosis factor α are involved in the pathogenesis of psoriasis. The anti-inflammatory effect of progranulin (PGRN) is known by inhibiting the effects of Tumor Necrosis Factor (TNF- α). We aimed to evaluate the PGRN levels and the factors affecting PGRN levels in patients with psoriasis. **Materials and Methods:** The study enrolled 44 patients with psoriasis and 44 age- and sex- matched healthy controls. Serum PGRN levels were measured in all participants and compared between the two groups. PGRN levels were also evaluated in terms of demographic data, duration of disease, age of onset, previous treatments, smoking and drinking habits, PASI scores, and presence of nail and joint involvement in the psoriasis group. **Results:** Mean serum PGRN levels were significantly higher (10.70 ± 2.56ng/ml) in the psoriasis group than in the control group (3.16 ± 1.02ng/ml) ($P < 0.001$). There was no significant relationship between serum PGRN levels and clinical characteristics of psoriasis including the presence of joint and nail involvement, PASI scores, duration of disease, age of onset. **Conclusions:** In conclusion, psoriasis patients have elevated serum levels of PGRN irrespective of patient and clinical characteristics. To increase knowledge on the effect of PGRN in the pathogenesis of psoriasis can lead to new therapeutic options for the disease.

Keywords: PASI, progranulin, psoriasis

Introduction

Psoriasis is a complex immune-mediated inflammatory disorder with a chronic course. The pathogenesis of the disease is still not fully understood though current concepts of the pathogenesis of psoriasis focused primarily on the immune dysregulation. Recent reports have indicated that interactions between the keratinocyte-released cytokines and keratinocytes, dendritic cells, T cells, and neutrophils contribute to triggering of cutaneous inflammation of psoriasis.[1]

Progranulin (PGRN) is known as proepithelin that is secreted as precursor glycoprotein which is an autocrine growth factor.[2,3] Progranulin is highly expressed in immune cells *in vivo* and in specific neurons in the brain, including Purkinje cells, pyramidal cells of the hippocampus, and some cerebral cortical neurons also epithelial cells and macrophages. In addition, low expressions of PRGN have been detected in muscle, connective tissue, or endothelium. PGRN has both inflammatory and anti-inflammatory functions.[4,5] PGRN has been considered a physiological tumor necrosis factor TNF 1 and TNF 2 receptor blocker. Therefore, the anti-inflammatory effects of PGRN are thought to be mediated by TNF receptors. It has been shown that ATSTTRIN, which is a synthetic derivative molecule of PGRN, exerts potent anti-inflammatory ability via binding TNFR.[6-9] Considering the main effects of PGRN on TNF receptors which plays role in psoriasis may suggest the possible role of anti-inflammatory effects of PGRN on psoriasis rather than inflammatory effect.

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Address for correspondence: Dr. Ömer Kutlu, Tokat Gaziosmanpaşa University, School of Medicine, Department of Dermatology and Venereology, Tokat, Turkey.
E-mail: omerkutlu22@gmail.com

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TNF-α is a considered one of the key inflammatory cytokines along with IL-17, IL19, IL-23 in the pathogenesis of psoriasis.[1] The important role of TNF-α in psoriasis has been supported by the clinical experience regarding therapeutic efficacy of TNF-α blockers in the treatment of psoriasis. In addition, recent studies have focused on determining whether PGRN could be a therapeutic target for immune-mediated inflammatory disorders such as inflammatory bowel disease, rheumatoid arthritis, and multiple sclerosis that share common immunological pathomechanisms of psoriasis.[4,10,11] Given these findings, we aimed to investigate whether serum PGRN level is elevated in psoriasis patients and is correlated with disease characteristics and activity.

Materials and Methods

Participants and study protocol

In this case-control study, we enrolled patients who have psoriasis at dermatology outpatient clinics of Ankara Numune Training and Research Hospital between September 2016 and September 2017. A total of 88 participants including 44 patients with psoriasis and 44 age- and sex-matched healthy controls (HCs) were recruited in this study. Inclusion criteria were patients with age of ≥18 years and agreement to participate in the study for both groups. Exclusion criteria were pregnancy/lactation and having chronic systemic inflammatory disease or malignancy and patients who had been treated for psoriasis with systemic drugs and/or phototherapy in the preceding 3 months. Participants with a family history of psoriasis and/or psoriatic arthritis were not included as HCs.

Demographic data including age, sex, personal and family medical history, smoking, and drinking habits were recorded for all participants. The severity of psoriasis was assessed according to the psoriasis activity score index (PASI) while psoriatic arthritis was determined according to the classification criteria for psoriatic arthritis (CASPAR).

Measurement of PGRN levels

A venous blood sample (10 mL) was taken from each participant. Blood samples were centrifuged at 3500 g and separated sera were stored at -80°C until the time of analysis. PGRN levels were detected with double-antibody sandwich ELISA technique (Boster Biological Technology, Ltd. Wuhan, China) according to the manufacturer's recommendations, and PGRN levels were detected by micro-ELISA reader at 450 nm.[12]

The study was approved by Ankara Numune Training and Research Hospital Ethics Committee of Clinical Studies and conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Statistical analyses

Statistical analyses were performed using SPSS software (version 23.0 for Windows; SPSS Inc., Chicago, IL, USA). Parametric variables were determined as means and standard deviations while nonparametric variables are shown as medians and interquartile ranges (IQRs). Frequencies and percentages were calculated for the categorical variables. Chi-square or Fischer's exact test was used for analyzing the categorical variables. Normally distributed numeric variables were analyzed using the Student T-test and analysis of variance. Mann-Whitney U and Kruskal Wallis tests were used for comparing the non-normally distributed numeric variables. Correlations of numeric variables were assessed using Spearman and Pearson tests. Linear regression analysis was used to determine the relationship between the dependent and a single independent variable. P values <0.05 were considered to be significant.

Results

The mean age of patients with psoriasis was 30,5 ± 13,1 years while HCs was 40,1 ± 11,4 years. In addition, the patient with psoriasis has an average disease duration of 9 years and a family history of 15 patients. Psoriatic arthritis and nail involvement were found in 12 of 44 patients. The mean PASI scores of patients with psoriasis were 12,8.

There were no statistical differences between two groups in terms of age and sex. The clinical characteristics of the patients with psoriasis and demographic, habitual characteristics of both groups are summarized in Tables 1 and 2.

Mean serum PGRN levels were higher in patients with psoriasis (10.70 ± 2.56ng/ml) compared with HCs (3.16 ± 1.02 ng/ml) (P < 0.001). Comparison of PGRN levels of both groups is shown in Figure 1.

Serum PGRN levels were analyzed in terms of the clinical characteristics of patients with psoriasis. No statistically significant difference was found between serum PGRN levels and clinical characteristics of patients including gender, habitual characteristics, nail and/or joint involvement, duration of disease and patients who had been previously treated for psoriasis [Table 3]. Serum PGRN levels did not correlate with PASI scores of the patients (P > 0.05).The correlation between duration of psoriasis, the onset of disease, the age of patients and serum PGRN levels was showed in Table 4.

Overall psoriasis group was assessed regarding factors affecting the serum PGRN concentrations. Based on regression analysis there was an association between getting psoriasis and higher PGRN levels (P < 0.001) while there was no significant association between higher PGRN levels and age, gender, and habitual status [Table 5].

The regression analyses was performed in order to determine the independent effect of psoriasis on progranulin levels. Age, gender, smoking, and alcohol usage was added to the regression equation. When these

Table 1: Comparison of demographic characteristics and habitual status of psoriasis and control group

	Control group		Psoriasis group		*p*-values
	n (44)	%	n (44)	%	
Gender					1.000
Female	18	40.9%	18	40.9%	
Male	26	59.1%	26	59.1%	
Habit of cigarette smoking					0.257
Never smoked	32	72.7%	27	61.4%	
Current smoker	12	27.3%	17	38.6%	
Alcohol consumption					0.007
Ever used	43	97.7%	35	79.5%	
Social drinking	1	2.3%	9	20.5%	

n: number

Table 2: Clinical details of patients with the diagnosis of psoriasis ($n = 44$)

Parameters	Results
Age of disease onset (years)(mean±SD)	30.48 ± 13.15
Disease duration (years) (mean±SD)	9.02 ± 7.23
Family history of psoriasis (n [%])	15 (34.1%)
Nail involvement (n [%])	12 (27.3%)
Presence of psoriatic arthritis (n [%])	12 (27.3%)
PASI score(mean±SD)	12.08 ± 6.36
Previous treatment options* (n [%])[α]	
Topical treatments	41 (93.2%)
Phototherapy	7 (15.9%)
Systemic treatments	
Acitretin	5 (11.4%)
Methotrexate	10 (22.7%)
Cyclosporine	5 (11.4%)

*41 patients were treated previously. [α]Some patients received >1 treatment option.

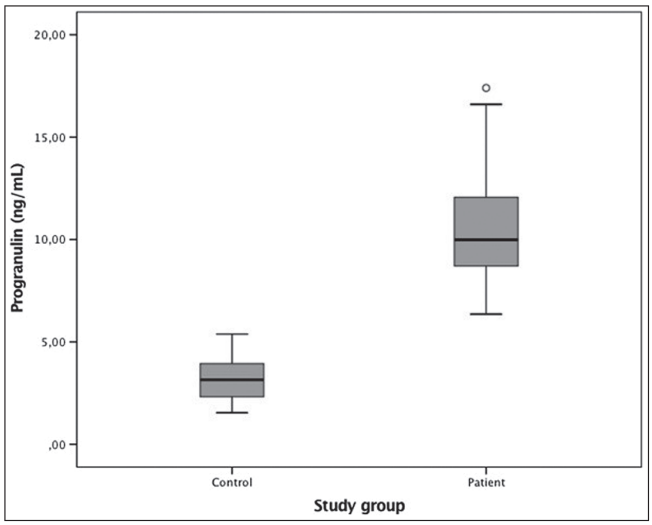

Figure 1: Comparison of PGRN levels in patient and control groups

factors were analyzed together, psoriasis was found as an independent factor that can increase the progranulin levels (B=7.53; t=17.395; $P < 0.001$).

Discussion

Progranulin has recently been extensively investigated in the pathogenesis of auto inflammatory and autoimmune diseases. However, the exact role of PGRN in psoriasis vulgaris is still unknown. Huang *et al.* reported that there was a statistically higher mean serum level of PGRN in 34 patients with psoriasis than in 20 HCs. In addition, they demonstrated a negative correlation between PASI score and PGRN/TNF-α levels. Authors have also shown that serum levels of PGRN decrease in patients treated appropriately.[13]

In our study, we detected significantly elevated levels of PGRN in patients with psoriasis, however, we could not find a significant positive or negative correlation between PASI scores and PGRN levels. In the study of Tian *et al.* the levels of PGRN were remarkably increased in skin samples of psoriasis patients compared to the skin samples of HCs. Wnt/ β-catenin signal pathway plays pro-inflammatory role in the psoriasis pathogenesis. It is noteworthy that previous study revaled increasing levels of PGRN expression in cultured cells that resulted in inhibiton of Wnt/ β-catenin signal pathway.[5] Based on these findings, we considered that PGRN may have anti-inflammatory effect in patients with psoriasis.

In recent years, anti-inflammatory effects of keratinocytes autophagy has been emphasized in the pathogenesis of psoriasis. It has been reported that as the PGRN expression attenuates in psoriatic lesions keratinocytes autophagy markers decreases.[4,5] Thus, besides anti-inflammatory effects, elevated PGRN levels in psoriatic lesions may increase keratinocytes autophagy that resulted in anti-inflammatory properties.

In another study, Farag *et al.* found that tissue PGRN expression was significantly increased in lesions of psoriasis along with perilesional skin when compared to the control group. It is important that PGRN expression increases as psoriasis severity increases.[14] In this regard, serum PGRN levels may be useful biomarker in psoriasis since PGRN may play a central role in psoriasis.

Table 3: PGRN levels of patients according the characteristics of the patients

	Progranulin (ng/mL)					
	Mean	SD	Median	Minimum	Maximum	*p*
Gender						
Female	10.21	2.42	9.66	6.64	16.60	0.377
Male	11.04	2.64	11.12	6.36	17.40	
Cigarette smoking						
No	10.18	2.25	9.86	6.64	16.60	0.085
Yes	11.52	2.86	11.54	6.36	17.40	
Alcohol consumption						
No	10.68	2.57	9.90	6.64	17.40	0.782
Yes	10.78	2.64	11.54	6.36	15.46	
Family history						
No	10.91	2.83	10.04	6.36	17.40	0.465
Yes	10.28	1.93	9.38	8.36	13.94	
Presence of previous treatments						
No	9.91	3.08	11.54	6.36	11.84	0.798
Yes	10.76	2.55	9.94	6.64	17.40	
Nail involvement						
No	11.00	2.73	10.78	6.36	17.40	0.268
Yes	9.89	1.88	9.30	7.46	13.94	
Psoriatic arthritis						
No	10.99	2.6	10.78	6.36	17.40	0.133
Yes	9.92	2.35	8.85	7.46	15.46	

Table 4: Correlation between serum PGRN levels and characteristic of disease

	PGRN (ng/mL)	
	r	*p*
Duration of psoriasis (year)	-0,168	0,275
The onset of disease	-0,231	0,132
The age of patients	-0,047	0,666

It has been shown that anti-inflammatory effect of PGRN is caused by direct inhibition of TNF-α receptors including TNFR1 and TNFR2.[14,15] PGRN antibodies (PGRN-Ab) are capable of neutralizing effects of plasma PGRN levels.[15,16] Thurner *et al.* have demonstrated serum PGRN-Abs exist 19% of psoriasis patients with psoriatic arthritis.[16] These patients had lower levels of serum PGRN while a higher frequency of dactylitis/enthesitis. Interestingly, none of patients without arthritic manifestation have not exhibited PGRN-Abs. There are various reports supporting these findings in other diseases that have a wealth of common pathogenic pathways with psoriasis.[10,11] In our study there were 12 patients with psoriatic arthritis. However, we could not find any statistical difference in serum levels of PGRN between patients with and without psoriatic arthritis.

The small number of subjects was the main limitation of our study. Therefore, the results of the study cannot be generalized to the general population. Since most of the patients in this study had been previously treated, we cannot draw a valid conclusion about the effects of drug therapies on PGRN levels. The lack of PGRN Abs levels was another limitation of this study.

Conclusions

In conclusion, we found that patients with psoriasis have higher levels of PGRN irrespective of age, gender, habitual characteristic and clinical characteristics of the patients including PASI score and presence of arthritis. Considering these results PGRN seems to candidate novel an anti-inflammatory biomarker in the disease pathogenesis. In addition, PGRN-Abs may have prognostic value in more severe and recalcitrant forms of the disease. Future studies detecting the predictive value of PGRN-Abs may provide new insights for the management of psoriasis.

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Conflicts of interest

The authors whose names are listed immediately above certify that have no affiliations with or involvement in any organization

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Table 5: Regression analyses for serum PGRN levels in patients and HCs

	Unstandardized Coefficients		Standardized Coefficients	t	*p*-values
	B	Std. Error	Beta		
(Constant)	3.501	0.787		4.451	<0.001
Group (Patient/Control)	7.530	0.433	0.889	17.395	<0.001
Age	-0.020	0.017	-0.058	-1.179	0.242
Sex	0.463	0.444	0.054	1.044	0.300
Smoking status	0.740	0.460	0.082	1.608	0.112
Alcohol consumption	-0.461	0.734	-0.035	-0.628	0.532

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