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Detection of Some Immunological Parameters in Psoriatic Iraqi Female Patients

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Abstract

Psoriasis is a common, chronic, immune-mediated skin disease with systemic pro-inflammatory activation. This study was designed to estimate the level of two cytokines, Interleukin-36 (IL-36) and Interleukin-10 (IL-10), in psoriasis female patients. The study was accomplished on 50 Iraqi patients with psoriasis who were referred to the consulting clinic at Al-Yarmouk Teaching Hospital during the period from November 2018 to March 2019. These patients were diagnosed under the supervision of dermatologists. For the purpose of comparison, the study included 30 healthy women as a healthy control group. The serum levels of cytokines were measured using the enzyme-linked immunosorbent technique (ELISA).The results of this study showed that the mean age of the female patients was 35.9 ± 1.85 years, whereas the age of the patients with a severity of higher than 30% ranged 15-25 years. Most of the patients were married, in an average living condition, and non-smokers, and their menstrual cycle was continuous. It was also found that 28% of the psoriatic patients had other chronic diseases. The study showed statistically significant differences ($p < 0.05$) in the mean level of IL-36 between the patients and healthy control group, whereas there was no statistical difference in the mean level of IL-10. In conclusion, the decrease in the level of IL-36 in the patients might be related to the increase in the severity of the disease.

Keywords: Psoriasis, Interleukin-36, Interleukin-10.

البحث في بعض المعايير المناعية لإناث مصابات بمرض الصدفية

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الخلاصه

الصدفية هي مرض مناعي جلدي شائع مزمن يتميز بنشاط النظام الالتهابي. تم تصميم هذه الدراسة لتقدير مستوى بعض السيتوكينات البين الابيضاضي- 36 و البين الابيضاضي- 10 في مريضات الصدفية. أجريت هذه الدراسة على 50 مريضة عراقية مصابة بالصدفية تم إحالتهن إلى العيادة الاستشارية في مستشفى اليرموك التعليمي خلال الفترة من تشرين الثاني 2018 لغاية آذار 2019. وقد تم تشخيص هؤلاء المرضى تحت إشراف الأطباء في الأمراض الجلدية. ولغرض المقارنة ، شملت الدراسة 30 امرأة سليمة كمجموعة السيطرة الاصحاء. تم قياس مستوى السيتوكينات (البين الابيضاضي- 36، والبين الابيضاضي- 10) باستخدام تقنية الممتز المناعي المرتبط بالانزيم (ELISA). والنتيجة في هذه الدراسة اظهرت أن متوسط عمر المرضى الإناث كان 35.9 ± 1.85 سنة، وكانت أعمار الأشخاص الاكثر اصابة اللواتي ضمن الدراسة

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تتراوح بين الفئة العمرية (15−25) سنة بنسبة 30%. معظم المريضات كانوا من المتزوجات وفي حالة معيشية متوسطة، وغير مدخنات ، وكانت الدورة الشهرية أيضًا مستمرة لديهن. في حين وجد ان 28 % من مريضات الصدفية لديهن أمراض اخرى مزمنة . وفقا لنتائج مستويات المصل، أظهرت الدراسة الحالية أن هناك فروق ذات دلالة إحصائية ($p-value$ <0.05) في متوسط مستوى البين الابيضاضي− 36 بين مرضى الصدفية ومجموعة السيطرة الاصحاء. في حين لا يوجد فرق احصائي ($p-value$ > 0.05) في متوسط مستوى البين الابيضاضي 10− بين مرضى الصدفية ومجموعة السيطرة الاصحاء. نستنتج من هذا ان انخفاض في مستوى البين الابيضاضي− 36 في المرضى مقارنة بمستواه في الأشخاص الأصحاء، قد يكون مرتبط بزيادة في شدة المرض.

Introduction

Psoriasis is a chronic inflammatory (immune-mediated) skin disease, affecting approximately 2-3% of the world's population. While it is more common in Caucasians, it can affect any race and can occur at any age, being recognized by a change in the proliferation and differentiation of keratinocytes [1, 2]. Psoriasis is also characterized by the inflammation and scaling of the skin [3]. The disease is caused by the association of distorted keratinocytes and improper innate and adaptive immune responses. The causes of the defect in the keratinocytes are not known, but the evidence indicated that genetic, environmental, and immunological factors play important roles in the development of psoriasis [3, 4].

The dysregulated interactions of the innate and adaptive immune responses that are associated with psoriasis affect the epithelial and connective tissues of the skin [5]. Psoriasis is also characterized by an increased activation of T lymphocytes and systemic and local overexpression of pro-inflammatory cytokines such as interleukin 2 (IL-2), gamma interferon (IFN-γ), interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) [6].

Interleukin-36 (IL-36) is a member of the IL-1 superfamily, which has four existing isoforms [7], assigned as IL-36α, IL-36β, IL-36γ, and IL-36 receptor antagonist (Ra) [8]. IL-36 is increasingly associated with inflammatory diseases, including various inflammatory and infectious skin disorders [9]. Among these, psoriasis is the most prominent skin disease associated with IL-36 [10].

Interleukin-10 (IL-10) is a cytokine with anti-inflammatory properties that has a central role in infections by limiting the immune response to pathogens and thereby preventing damage to the host [11]. It also has a crucial role in preventing inflammatory and autoimmune pathologies [12]. Long-term application of IL-10 in psoriatic patients showed that it had moderate anti-psoriatic effects, was well tolerated, decreased the incidence of relapse, and prolonged the disease-free interval [13]. The pathogenesis of psoriasis and other autoimmune diseases involves a genetic background and environmental triggers. Like other autoimmune diseases, psoriasis was shown to have a strong genetic component, with a concordance rate in identical twins of 40-70% [1, 3].

This study aimed to evaluate the levels of both IL-10 and IL-36 that might be associated with the exacerbation of psoriasis in Iraqi patients.

Materials and Methods

Subjects

A sample was collected from patients suffering from severe or moderate psoriasis. The study included 50 Iraqi female patients in Al-Yarmouk educational hospital during the period from November 2018 to March 2019, while another group consisted of 30 healthy females as a control. The patients were treated with classical psoriasis treatments, such as biological (pills or injections) and chemical therapy. The complete history of illness in the patients was recorded in a questionnaire sheet.

Blood sampling

Five milliliters of blood were collected by vein puncture from all patients and control subjects. The blood was allowed to coagulate for 10-20 minutes at room temperature and centrifuged at 2000-3000 rpm for 15 minutes. The collected serum was distributed in three to four Eppendorf tubes and kept at a temperature of -20 ° C to be used later.

Measurements of immunological and biochemical parameters

Serum levels of Cytokines (IL-36 and IL-10) were measured using the ELISA kit from Elabscience, USA, following the steps in the manufacturer's protocol.

Statistical analysis

Comparisons of qualitative data were carried out using Chi-square test ($\chi 2$). While quantitative data were handled using ANOVA test. Statistical analysis was performed using the statistical package SPSS for Windows (version 23, SPSS Inc., Chicago, IL, USA). A probability value of less than 0.05) was adopted to indicate statistical significance for each test [14].

Results and Discussion

Description of the Studied Samples

The pictures in Figure -1 represent various pathological cases of psoriasis patients included in the study and note the differences in pathological severity. Demographical distribution of the studied groups according to different parameters (age, social status, living situation, being in the period, smoking, kinds of other chronic diseases, and the treatment used) is summarized in Table-1. The results clarified that the age ranged between 15-65 years and the mean age was 35.9±1.85 years. Most of psoriatic patients and control subjects were within the age group of 15-25 year (30% vs. 50 %,), while the lowest percentages were within the age group of 56-65 year. Also, it was found that about 54 % of psoriatic patients are married, 90 % with an average living situation, 64% with continuous period, 98 % none-smokers, 72 % have no chronic disease, and 76 % used treatments for other chronic diseases.

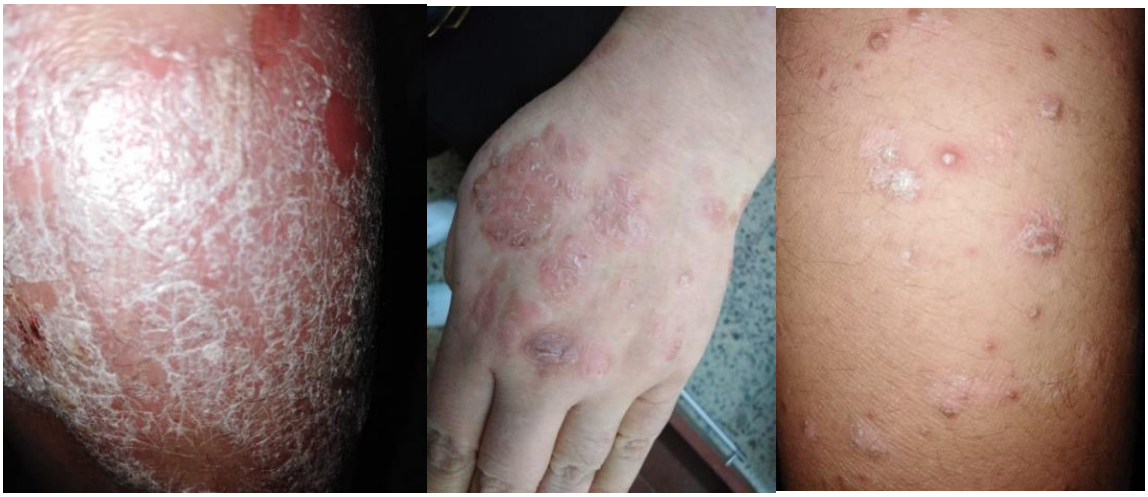

Figure 1- Images of various severity levels of psoriasis from different patients in the present study.

Many previous studies investigated the mean age in patients with psoriasis. One local study [15] and another one conducted in another country [16] showed similar mean ages of psoriasis patients as those found in the present study, being mostly within the second decade. Also, a study in Turkey reported that the mean age was 37.8 years [17], whereas 34.5 years was the mean age recorded in Northern India [18]. Psoriasis can occur at any age, while its prevalence increases with age and peaks between the second and third decades, usually because of wars in the past twenty years that caused major pollution events and, consequently, the appearance of several diseases [19]. Geographic location influences the likelihood of having psoriasis; disease prevalence tends to increase with increasing distance from the equator. Moreover, a systematic worldwide review found that the prevalence of psoriasis ranged from 0.5-11.4 % in adults and 0 -1.4 % in children. These differences are the result of differences in the region, the randomness of samples, and average age of the people in different countries [2].

Table 1- The percentage distribution of the studied groups according to different categories.

Variables	Status	Patient (N=50)			Control (N=30)		
		Frequency	mean± SEM	Percentage %	Frequency	mean± SEM	Percentage %
Age	15-25 year	15	35.9 ± 1.85	30	15	28.7 ± 1.73	50
	26-35 year	10		20	9		30
	36-45 year	13		26	4		13.3
	46-55 year	10		20	2		6.7
	56-65 year	2		4	0		0
Social status	Married	27		54	16		53.3
	Single	19		38	14		46.7
	Divorced	3		6	0		0
	Widow	1		2	0		0
Living situation	Good	3		6	7		23.4
	Average	45		90	19		63.3
	weak	2		4	4		13.3
The Menstrual	Continuous	32		64	22		73.3
	During period	5		10	7		23.4
	Stopped	13		26	1		3.3
Smoke	Smoker	1		2	3		10
	None	49		98	27		90
Kind of chronic disease	Found	14		28	8		26.7
	None	36		72	22		73.3
The used treatment of chronic disease	Used	12		24	8		26.7
	None	38		76	22		73.3

*SEM: Std. error of Mean.

Previous studies showed that 46.9% [20] and 55% [21] of psoriatic patients were females. Our results showed an interesting observation that higher (social class) living situation in psoriasis patients was very low compare with below social class, and represented a small low risk of psoriasis. Social class determines many lifestyle parameters that could be risk factors for psoriasis; these factors include smoking, stress, jobs, exposure to sunlight...etc. [20]. Disease flares are known to occur in stressful life situations and certain literature links psoriasis activity to stress from major life events [22].

Table 2- Values of different variables of psoriatic patients.

Group	Variables	Status	Frequency	Mean ± SEM	Percentage %
A	**Period of disease**	<1 year	3	8.14 ± 1.05	6
		1-10 year	32		64
		11-20 year	10		20
		21-29 year	3		6
		None	2		4
B	**Period of treatments**	<1 year	17	1.87 ± 0.47	34
		1-4 year	17		34
		5-8 year	6		12
		>8 year	1		2
		Continuous	8		16
		Intermittent	1		2
C	**The causes of disease**	After birth	5		10
		Hereditary	16		32
		Psychological state	28		56
		trauma	1		2
D	**The kind of treatment**	Biological injection	9		18
		Biological injection and Traditional drug	1		2
		Biological pills	31		62
		Chemical pills	1		2
		Traditional drug	8		16
Chi-square (X^2) test		**Groups**	***X^2***	***p-value***	**Sig.**
		A vas B	42.872	0.002*	Significant
		A vas C	9.992	0.617	None-Significant
		A vas D	5.263	0.994	None-Significant
		B vas C	10.069	0.815	None-Significant
		B vas D	16.653	0.675	None-Significant
		C vas D	12.39	0.415	None-Significant

*SEM: Std. error of Mean.

The pathological characteristics of the 50 patients with psoriasis (period of the disease, the period of treatments, the causes of disease, and the kind of treatment) are summarized in Table-2. The results clarified that the most patients (64%) had a period of 1-10 years since the first appearance of the disease, while the mean period was 8.14±1.05 years. The period of treatment was mostly lower than 1 year, with a range of 1-4 years in 34% of the patients, while the mean period of 1.87±0.47. Most of the patients (62) used biological pills, mainly cortisone, for treatment. The psychological state was the most affecting parameter (56%) for causing the disease. Also, 70% of the patients had the entire body infected by psoriasis. In addition, statically significant differences, as tested by Chi-square (X^2) test, were only recorded in the parameters of the period of the appearance of the disease and the period of treatments.

The defect in keratinocytes associated with psoriasis is caused by several factors including environmental, genetic, and immunologic. The environmental factors break the body balance to affect the onset and development of psoriasis. Other factors like psychological stress are widely believed to play a role, but evidence is controversial on whether the effects are on triggering or exacerbating the disease [4]. Also, family history (heredity) was found in about 30% of the patients, because of continuous exposure of human body cells to harmful agents, most of which are of oxidative kind, that have the ability to cause deoxyribonucleic acid (DNA) damage [23, 24]. Significant progress in understanding the pathogenesis and treatment of psoriasis has been made in the last several years [25].

Serum Levels of Cytokines

Serum Level of IL-36

The psoriatic patients showed a highly significant decrease ($p < 0.05$) in the mean of serum of IL-36 (64.74±1.09 pg/ml) compared with its level in the healthy control group (89.7±0.62 pg/ml), as shown in Figure-2.

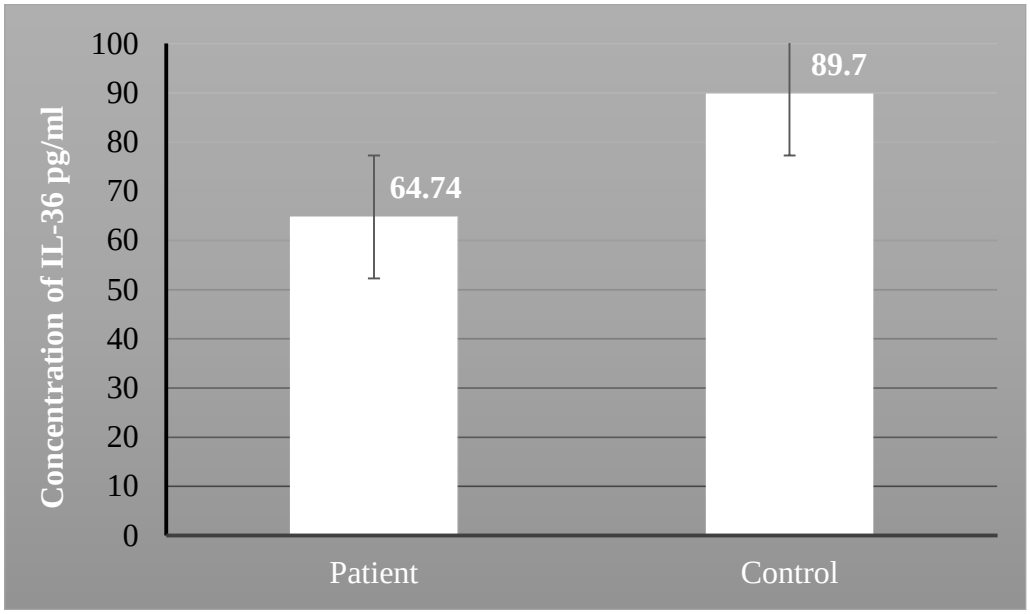

Figure 2- The mean serum level of IL-36 pg/ml in Psoriatic Patients and Healthy Control.

Previous studies showed a high increase of IL-36 level in non-treated psoriatic patients [10, 26, 27]. While, other studies found that serum levels of IL-36 were decreased under treatment [28, 29, 30]. IL-36 has important functions in the regulation of immune responses, especially its involvement in many inflammatory conditions. It activates similar intracellular signals as those activated by IL-1 and is involved in the regulation of innate as well as adaptive immune responses [9, 26, 31].

IL-36 cytokines are critical members of the cytokine milieu that drives skin inflammation in this model. IL-36 induces the expression of chemokines by keratinocytes and drives the activation of antigen-presenting cells (APCs) [9, 28, 32]. These observations are consistent with a role for IL-36 in driving psoriatic skin inflammation by attracting neutrophils, myeloid cells, and T cells into developing psoriatic lesions and altering APC function to potentiate the inflammatory cycle. In early experiments, microgram quantities of recombinant IL-36 ligands were required for inducing keratinocyte responses [10, 28].

The potential importance of the IL-36 family in psoriasis was high-lighted by the discovery that the loss-of-function mutations in the IL-36 receptor antagonist gene IL36RN underlie a rare but debilitating form of psoriasis, known as the generalized pustular psoriasis (GPP) [33, 34]. Such mutations leave IL-36 agonist activity unchecked, driving a neutrophilic skin inflammation. Although inhibition of the canonical IL-1 system has not proved to be an effective therapeutic approach in psoriasis [35], targeting the IL-36 system holds promise, particularly in the debilitating conditions of GPP and the closely-related disease palmar-plantar pustulosis (PPP), particularly where mutations in IL36RN have been identified. The involvement of IL-36 may not be restricted entirely to GPP and PPP, as psoriasis tends to occur across a spectrum of phenotypes, and the IL-36 system may play a greater role in the more neutrophilic forms of the disease [36]. Expression of IL-36 has been shown to be restricted to epithelial cells in direct contact with the environment, including the skin [28], which when taken together with the observations above highlight IL-36 as an attractive new therapeutic target for psoriasis [37].

Serum Level of IL-10

The mean serum level of IL-10 in psoriatic patients showed no significant differences when compared to its level in the healthy control, as shown in Figure-3. IL-10 serum levels in the patients and the healthy control group were 89.89±1.45 and 90.67±0.59 pg/ml, respectively.

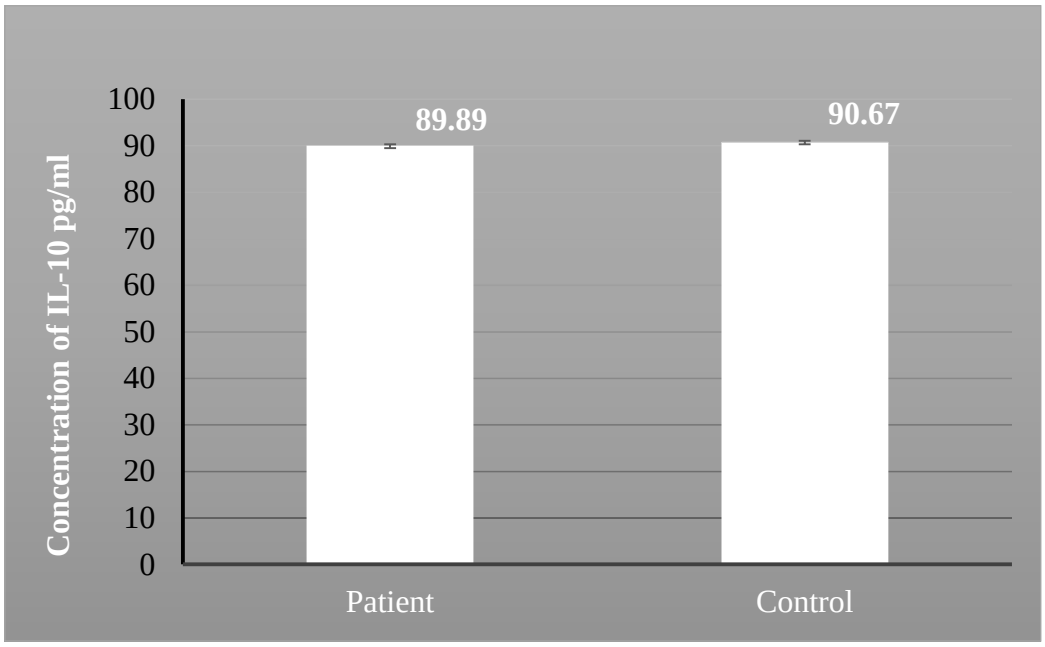

Figure 3- The mean serum level of IL-10 pg/ml in Psoriasis Patients and Healthy Control.

Previous studies reported extremely varied results for the roles of IL-10 in psoriasis. Verghese *et al*. and Khalaf reported that the mean values of IL-10 concentrations in the patients were non-significantly different from those in the control group [18, 15]. The results above are compatible with those of the current study. While another study by Borska *et al.* reported that IL-10 concentrations were significantly higher in psoriatic patients, while they were decreased after the treatment. Deeva *et al*. observed that moderate-to-severe psoriasis patients have a higher level of IL-10 [38, 39]. Few studies demonstrated a significantly decreased serum level of IL-10 in psoriatic patients [40, 41]. Although IL-10 plays an important role in the anti-inflammatory response in psoriasis, the serum levels of IL-10 in patients with psoriasis have been studied only rarely, and the results are contradictory [38].

The significant decrease in mean IL-10 concentration reported by some studies can be explained by a systemic functional deficiency of regulatory T cells, and the subsequent decrease of serum IL-10 levels that may predispose to psoriasis pathogenesis. Moreover, patients treated with topical treatments and with ultraviolet-B presented lower IL-10 levels than patients treated with systemic drugs [20-18]. Low levels of IL-10 was found in the cutaneous lesions of psoriatic patients; after a progressive disease, high levels of IL-10 can be found in the peripheral blood mononuclear cells [42, 43].

Correlation Coefficient between Interleukins

The results in this study presented no significant correlation between IL-36 and IL-10 levels in the patients (-0.131) as well as in the control (-0.032) groups, as seen in Table-3.

Table 3 - Correlation Coefficient between Interleukins in this Study

Interleukins	Patient		Control	
	Correlation coefficient	sig.	Correlation coefficient	sig.
IL-36 and IL-10	-.131	Non-Significant	-.032	Non-Significant

Association of Serum Levels of IL-36 and IL-10 with Different Varieties of Psoriatic Patients

The psoriatic patients were divided into different groups according to age, period since appearance of the disease, period of treatment, causes of disease, and kind of treatment. There was a significant association between IL-36 serum levels and age (p- < 0.05) but the association with serum levels of IL-10 was non-significant. While the associations of serum levels of IL-36 and IL-10 with all the other groups of patients were insignificant (Table -4).

Table 4- Values of IL-36 and IL-10 serum levels according to different varieties of Psoriatic Patients.

Variables	Status	IL-36 Mean±SEM	*p value*	IL-10 Mean ±SEM	*p value*
Age	15-25 year	69.6±1.9	0.05*	91.5±2.6	0.9
	26-35 year	62.9±1.4		91.2±3.6	
	36-45 year	61.5±1.6		88.2±3.2	
	46-55 year	64±3.2		88.6±2.9	
	56-65 year	62.5±3.5		88.5±7.5	
Period since appearance of disease	<1 year	64±6	0.45	86.7±3	0.11
	1-10 year	65.9±1.3		88.1±1.6	
	11-20 year	64.3±2.9		97.6±4.3	
	21-29 year	58±2		86±0.6	
	None	60±1		91±2	
Period of treatments	<1 year	63.7±2.2	0.76	91.1±2.5	0.42
	1-4 year	65±1.2		86.8±2.6	
	5-8 year	68.5±4.4		87.1±2	
	>8 year	59±0		89±0	
	Continuous	65±2.8		96±4.4	
	Intermittent	60±0		89±0	
The causes of disease	After birth	62.4±2.9	0.54	85.8±2	0.78
	Hereditary	65.2±1.9		90.9±3.7	
	Psychological state	65.2±1.5		90.2±1.5	
	trauma	55±0		86±0	
The kind of treatment	Biological injection	66.8±2.2	0.37	91.8±5	0.89
	Biological injection and Traditional drug	54±0		91±0	
	Biological pills	65.2±1.5		89.5±1.7	
	Chemical pills	55.8±0		97.4±0	
	Traditional drug	63.3±2		88.1±3	

Data presented as One-way ANOVA. *statically significant at *p-value* ≤0.05.

Conclusions

Psoriasis patients showed a significant decrease in the level of IL-36 as compared to its level in the healthy subjects. This decrease may be related to the increase in the severity of the disease. Therefore, it is necessary to conduct additional studies to investigate the levels of this cytokine in the affected skin, its role in the occurrence of the diseases, and the possibility of using it as an anti-psoriasis treatment.

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