



Serum level of interleukin-17 in patients with psoriasis

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Abstract

Introduction: Psoriasis is one of the most common chronic and disabling dermatoses. Recent studies showed that interleukin-17 (IL-17) may play a role in the development of psoriasis.

Objectives: In this study, serum levels of IL-17 in psoriatic patients was compared with healthy controls; besides, in patients with psoriasis, serum levels of IL-17 were compared with pre-treatment levels, after topical treatments.

Patients and Methods: In this case-control study, serum levels of IL-17 were measured and compared in 30 psoriatic patients and 30 healthy individuals matched to age, gender and body mass index. After evaluating the severity of psoriasis with PASI (Psoriasis Area Severity Index), they were treated with psoriasis topical corticosteroids for four weeks. IL-17 and PASI levels were re-evaluated after the treatment without any intervention.

Results: Before the start of treatment, the mean \pm SD of serum level of IL-17 was 6.24 ± 4.65 pg/mL and 2.0 ± 0.75 pg/mL in psoriatic patients and control group, respectively ($P=0.001$). The mean \pm SD of PASI severity scale of patients was 10.68 ± 6.65 and 6.16 ± 4.2 before and after treatment, respectively ($P<0.001$). The mean \pm SD of serum level of IL-17 of patients before and one month after treatment were 6.24 ± 4.65 and 3.34 ± 1.77 pg/mL, respectively.

Conclusion: In psoriatic patients, serum levels of IL-17 increased significantly compared to healthy subjects. Treatment of psoriasis with topical corticosteroids for four weeks reduced the serum level of IL-17 and the severity of disease.

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Introduction

Psoriasis is one of the most common persistent chronic and often debilitating skin diseases, characterized by erythematous plaques with white-silver scales covering various parts of the body, especially the extensor surfaces such as the elbow, knee, lumbosacral areas and scalp. Different forms of the disease include psoriasis vulgaris or plaque psoriasis, flexural or inverse, guttate, pustular and erythrodermic psoriasis, and also psoriatic arthritis. Plaque psoriasis is the most common form of psoriasis, approximately constitutes 90% of cases. According to reports, the prevalence of disease ranges 1-3% in different communities and males and females are affected equally. First-degree relatives of the psoriasis patients are at higher risk of disease. The etiology of disease is not exactly known; however, various causes including genetic, environmental and autoimmune factors are raised in its pathogenesis. Epidermal acanthosis along with regular elongation and clubbing of rete ridges, thinning of supra-papillary plates, parakeratotic hyperkeratosis, hypogranulosis,

Key point

Serum level of IL-17, as a pro-inflammatory cytokine, was higher in patients with psoriasis. Additionally, treatment of psoriasis with topical medications reduced serum levels of IL-17.

and Munro's microabscess are important diagnostic findings in histopathology (1,2).

The abnormal function of T-lymphocytes is one of the important issues in the pathogenesis of psoriasis related to the production of cytokines. Cytokines are small glycoproteins produced in response to various stimuli and regulate the function of immune cells by binding to specific receptors. Cytokines are functionally divided into two classes of anti-inflammatory and pro-inflammatory. The imbalance between these two groups is associated with allergic and autoimmune diseases. There is evidence that show unregulated production of cytokine may lead to an abnormal inflammatory response (3,4). Recent studies detected that interleukin-17 (IL-17) may play a role in the development

of psoriasis (5,6). IL-17 is a pro-inflammatory cytokine mostly produced by T-helper-17 (Th17) lymphocytes and stimulates macrophages, endothelial cells, fibroblasts and epithelial cells, leading to the secretion of some other pro-inflammatory cytokines including tumor necrosis factor (TNF)- α , IL-6, IL-1, chemokines and metalloproteinases (7,8). A subset of CD4+ T-cells including Th17 and natural cells such as $\gamma\delta$ are major producers of IL-17 (9,10). One of the treatments recently introduced for psoriasis is IL-17 inhibitors (1-3). Results of some studies on the recognition of IL-17 pathway show that biological therapies have led to new achievements in the treatment of recurrent psoriasis, thereby the administration of anti-IL-17, such as ixekizumab, improves the moderate to severe symptoms of psoriasis (4,6).

These ideas have led researchers to provide a better perception of the complex pathogenesis of psoriasis in terms of immune changes. Accordingly, one of the most recent and perhaps most promising innovations in psoriasis research is based on the evaluation of cytokines related to CD4+ lymphocytes, especially Th17, and its effects on the pathophysiology of the disease. Given the high prevalence of psoriasis and the inadequate response of the disease to the current treatments in some cases, research is needed to investigate this issue, in different communities.

Objectives

The current study aimed at determining the serum levels of IL-17 in patients with psoriasis before and after topical steroid therapy and its relationship with disease severity.

Patients and Methods

Study design

This case-control study is designed to evaluate serum level of IL-17 of psoriatic patients, in comparison with those of a control group. In the current study, patients with psoriasis referred to dermatology clinic at Sina hospital of Hamadan (in northwest of Iran), were selected based on definite clinical and pathological criteria. The study was conducted in 2017. The patients should have active psoriatic skin lesions and a history of disease, without recent use of topical or systemic corticosteroid in the last three months. After explaining the study protocol and obtaining written informed consent, the participants were enrolled in the study. In addition, subjects with a history of concomitant autoimmune or inflammatory diseases, and also pregnant or lactating women were excluded. Healthy subjects (the control group) were selected from non-familial companions referred to the clinic if they had no history of autoimmune or inflammatory diseases. It should be noted, the case and control groups were matched for age, gender and body mass index.

Demographic and clinical data including age, gender, duration of disease, drug history, past medical history, type of psoriasis and severity of disease were recorded by a qualified dermatologist in a researcher-designed

questionnaire. Disease severity was measured by the PASI (Psoriasis Area and Severity Index) (5). [Table 1](#) is based on the intensity and extent of skin lesions, [from zero (no disease) to 72 (maximum disease)].

To measure serum level of IL-17, venous blood samples (5 cc) were collected under aseptic conditions from both groups and from psoriatic patients four weeks after treatment in one run after storage of serum at -70°C . Serum levels of IL-17 were measured at 450 nm wavelength using a Stat Fax 3200 ELISA (enzyme-linked immunosorbent assay), Reader and Invitrogen High-Sensitivity IL-17A Human ELISA kit (Thermo Fisher, USA) with detection range of 0.23-15 pg/mL, the analytical sensitivity of 0.01 pg/mL and the inter-assay coefficient of variation (CV) of 6.3%. A medical-lab-expert, blind to patients' PASI scores, conducted the experiments. Routine topical treatment of psoriasis including Eucerin-Urea ointment and 0.125% fluocinolone cream for trunk and limb lesions, and 0.05% betamethasone lotion for scalp lesions were prescribed to all patients nightly for one month; afterwards, patients were called for the evaluation of therapeutic response and second blood sampling. Those lost to follow-up and second blood testing or demonstrated non-compliance with specified treatment were excluded. All eligible patients referring to clinic of dermatology were selected by census method, due to the limited number of cases. Accordingly, a total of 38 eligible patients were selected, of which 30 completed the requested treatment; besides, 30 healthy individuals were included as the control group.

Data analysis

To analyze data, Statistical Package for the Social Sciences (SPSS) version 16 was applied. For analytical statistics, demographic and baseline characteristics of the groups including age, gender and body mass index (BMI) were evaluated in terms of confounding variables and both groups were homogeneous. The Kolmogorov-Smirnov test was conducted to determine the normality of the data. The Mann-Whitney U nonparametric test was utilized to compare serum IL-17 levels between patients and healthy controls and the Wilcoxon test was employed to compare serum IL-17 levels before and after routine treatment of psoriasis. Pearson's correlation coefficient was employed to determine the correlation of IL-17 levels with age, duration of disease and PASI score and chi-squared test was used to compare nominal qualitative variables in the two groups. P value <0.05 was considered the level of significance.

Results

In the current study, 30 patients with psoriasis and 30 healthy controls (totally 60 subjects) were studied. The mean age \pm standard deviation (SD) of the patients and healthy controls were 47.67 ± 12.39 years and 47.13 ± 12.67 years, respectively ($P=0.870$). The number of male and female subjects was 20 and 10 in the patients' group respectively, while it was 21 and 9 in the control group,

since both groups were homogeneous in terms of gender ($P=0.781$). The mean \pm SD of BMI for patients and healthy controls were 26.15 ± 5.09 kg/m² and 25.17 ± 3.16 kg/m², respectively ($P=0.378$). In addition, the severity of the disease, based on PASI, was 10.68 ± 6.65 before intervention and the duration of the disease was 5.9 ± 6.2 years in patients. The median of duration of disease was three years (Minimum: one year, Maximum: 30 years) in patients.

According to the Table 2, mean \pm SD of serum level of IL-17 in the patient (before intervention) and control groups were 6.24 ± 4.65 pg/mL and 2.0 ± 0.75 pg/mL, respectively. Accordingly by Mann-Whitney U nonparametric test, a significant difference between the groups was seen, while the level of this biomarker was higher in the psoriatic patients ($P<0.001$).

According to Table 3, the mean \pm SD of serum level of IL-17 of patients before and one month after treatment were

6.24 ± 4.65 pg/mL and 3.34 ± 1.77 pg/mL, respectively. According to the results of the Wilcoxon nonparametric test, the mean serum levels of IL-17 reduced significantly after intervention in psoriatic patients ($P<0.001$).

Mean serum levels of IL-17 were 6.42 ± 4.73 pg/mL and 5.89 ± 4.74 pg/mL in male and female patients before treatment, respectively since there was no significant difference between the genders (Mann-Whitney U; $P=0.914$). Additionally, mean serum levels of IL-17 in male and female patients were respectively 2.96 ± 0.99 pg/mL and 4.09 ± 2.6 pg/mL after treatment (T-test; $P=0.220$).

According to Table 4, among age, duration and severity of the disease, a significant and inverse correlation was found only between age and serum levels of IL-17 before treatment, (Pearson's correlation coefficient; $r=-0.364$, $P=0.048$; Figure 1). However, no significant correlation between serum levels of IL-17 and duration of the disease, before treatment was observed ($r=0.076$, $P=0.694$). In

Table 1. Calculation of psoriasis area and severity index (PASI)

	Severity of psoriatic lesions ^a			
	Head	Trunk	Upper limbs	Lower limbs
Erythema	0 to 4	0 to 4	0 to 4	0 to 4
Induration	0 to 4	0 to 4	0 to 4	0 to 4
Scaling	0 to 4	0 to 4	0 to 4	0 to 4
Total score=1	Sum of the above	Sum of the above	Sum of the above	Sum of the above
Area of psoriatic involvement ^b				
Degree of involvement=2	0 to 6	0 to 6	0 to 6	0 to 6
Multiply 1×2	1 × 2	1 × 2	1 × 2	1 × 2
Correction factor for area of involvement=3	0.10	0.30	0.20	0.40
1 × 2 × 3	A	B	C	D
A + B + C + D = total PASI				

^a [0, None; 1, Slight; 2, Moderate; 3, Severe; 4, Very severe].

^b [0, None; 1, <10%; 2, 10% to <30%; 3, 30% to <50%; 4, 50% to <70%; 5, 70% to <90%; 6, 90-100%]

Table 2. Comparison of serum level of interleukin 17 in patients with psoriasis (before treatment) and healthy subjects

Group	Number	Mean of IL-17 (pg/mL)	SD (pg/mL)	P value
Psoriatic patient	30	6.24	4.65	<0.001
Healthy control	30	2.00	0.75	

Table 3. Comparison of serum level of interleukin 17 in patients with psoriasis before and one month after starting treatment

Group	Number	Mean of IL-17 (pg/mL)	SD (pg/mL)	Z	P value
Before starting treatment	30	6.24	4.65	-4.43	<0.001
One month after treatment	30	3.34	1.77		

Table 4. Correlation coefficient between Serum level of interleukin 17 and age, duration and severity of disease (based on PASI) in patients with psoriasis before and after treatment

Time of sampling	Variables	r	P value
Before starting treatment	Serum level of interleukin 17- Age	-0.364	0.048
	Serum level of interleukin 17- Duration of disease	0.078	0.694
	Serum level of interleukin 17- Severity of disease	0.241	0.200
One month after treatment	Serum level of interleukin 17- Age	-0.241	0.197
	Serum level of interleukin 17- Duration of disease	-0.032	0.871
	Serum level of interleukin 17- Severity of disease	0.190	0.313

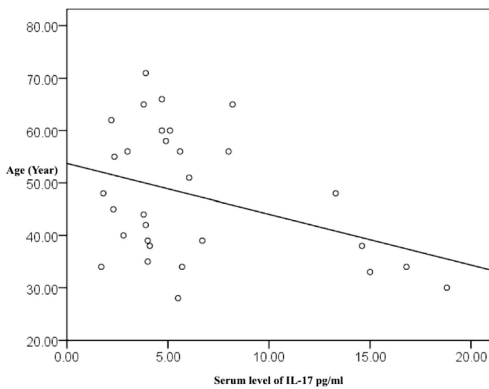


Figure 1. Inverse correlation between age and serum levels of IL-17 before treatment, (Pearson's correlation coefficient; $r = -0.364$, $P = 0.048$).

addition, no significant correlation between serum levels of IL-17 and severity of the disease (based on PASI score), before treatment was detected ($r = 0.241$, $P = 0.200$).

Along with the results of Pearson's correlation coefficient, no significant relationship between age, duration and severity of the disease, and also serum levels of IL-17 after treatment was found (Table 4).

Of 30 patients undergoing intervention, the post-intervention PASI score did not increase in any of them compared to pre-intervention scores. The pre-intervention and post-intervention PASI scores were equal in one case (3.33%), while it decreased compared to pre-intervention in the other 29 cases (96.67%) by 0.5 to 17 points.

According to the results of Table 5, the mean \pm SD of the disease severity based on PASI, were 10.68 ± 6.65 and 6.16 ± 4.2 before and one month after treatment, respectively; indicating a 42% decrease in the severity of the disease, on average. In other words, the severity of psoriasis significantly decreased one month after treatment with 0.125% fluocinolone cream and 0.05% betamethasone lotion ($P < 0.001$).

Discussion

Psoriasis is an immune-mediated inflammatory disease that can affect the skin, joints and nails and might be associated with other autoimmune diseases. Numerous studies evaluated serum levels of circulating cytokines in patients with psoriasis and compared the results with those of healthy controls. In the present study, the mean serum levels of IL-17 were significantly higher in patients than in healthy controls. Studies conducted by Sabri et al (7), Takahashi et al (8), EL-Moaty Zaher et al (10), de Oliveira et al (9), Caproni et al (11), and Suarez-Farinas et al (12), compared age- matched and gender-matched case

and control groups. The results of their studies showed, the serum levels of IL-17 was significantly higher in patients with psoriasis than healthy controls, which is consistent with the findings of the present study. However, in studies by Kyriakou et al (13), Arican et al (14), Yilmaz et al (15) and Michalak-Stoma et al (16), no significant difference was observed in serum levels of IL-17 between patients with psoriasis and the healthy controls. Differences among the results of the aforementioned studies could be due to different inclusion criteria, such as, the severity and duration of psoriasis and also the polymorphism of genes involved in psoriasis and cytokine genes in different populations. Moreover, in the present study, the severity of the disease, based on PASI score, was 10.68 before treatment and the duration of the disease was 5.9 years. While, in the study by Kyriakou et al (13), the mean PASI score was 4.10 and the mean duration of the disease was 11 years.

In the present study, no correlation was found between gender, duration of the disease and the severity of psoriasis, and also serum levels of IL-17; however, serum levels of IL-17 decreased significantly with increasing age. The study by de Oliveira et al (9), precluded the association of serum levels of IL-17 with age of psoriatic patients. In the current study, there was a significant and inverse correlation between age and serum levels of IL-17 before treatment, but no significant correlation was found with after treatment serum levels.

The results of previous studies are contradictory on the relationship between serum level of IL-17 and the severity of psoriasis based on PASI. Consistent with the current study results, Kyriakou et al (13), EL-Moaty Zaher et al (10) and de Oliveira et al (9) also excluded the association of serum levels of IL-17 with severity of psoriasis, since in studies by Takahashi et al (8), Arican et al (14), and Michalak-Stoma et al (16), a significant association was observed between the severity of psoriasis and serum levels of IL-17, therefore with increasing the severity of disease, the serum levels also increase. Different results might be attributed to the frequency distribution of the severity of psoriasis in the populations studied. Nevertheless, it should be noted, serum levels of IL-17 may be associated with extra-cutaneous manifestations of psoriasis or concomitant subclinical autoimmune diseases, whereas PASI focuses solely on the skin manifestations of the psoriasis. Another noteworthy point regarding the contradictory results of various studies is the non-linearity of the PASI, despite its prolific use in clinical trials. In other words, improvement in the severity of disease base on PASI cannot linearly reflect improvement in psoriasis that was emphasized in

Table 5. Comparison of the severity of psoriasis (based on PASI) before and after treatment by Fluocinolone ointment 0.125% and Betamethasone lotion 0.05%

Time of evaluation	Number	Mean of PASI	SD	Min	Max	t	P value
Before starting treatment	30	10.68	6.65	0.8	26.30	5.80	<0.001
One month after treatment	30	6.16	4.2	0.2	15.90		

studies by Puzenat et al (17), Spuls et al (18), and Carlin et al (19). It is also stated that PASI scoring system lacks adequate sensitivity in lower ranges, while has excessive sensitivity in higher ranges.

Despite the results of previous studies and our study on the lack of association between the severity of psoriasis and serum levels of IL-17, studies by Arican et al (14), Lowes et al (20) and Johansen et al (21) noted increased mRNA expression and accumulation of proteins related to this cytokine in skin biopsy specimens of psoriatic patients. This may indicate local activity of IL-17 at the site of skin lesion, regardless of its serum levels, involved in the progression of psoriasis (1, 3). Nevertheless, the findings of the study by Kim et al (22) are also noteworthy in this realm. They compared patients with mild psoriasis and mean PASI score of 5.5 with the ones with severe psoriasis and the mean PASI score of 23.2. Their results showed, higher number of T-lymphocytes and higher expression of IL-17A in mild skin lesions versus lack of their increase in the severe form of the disease. They noted, higher expression of negative immune regulatory genes in mild skin lesions compared to severe form of the disease. The overall findings indicated the complexity of the molecular pathway of IL-17 in the pathogenesis of psoriasis, indicating the need for more detailed studies in this field.

Although our study indicated lack of association between the severity of psoriasis and serum levels of IL-17, its important finding was a significant decrease in serum levels of IL-17 and severity of psoriasis following a one-month treatment with topical fluocinolone and betamethasone. This reflects the value of serum levels of IL-17 as a biomarker for the evaluation of the response rate in psoriasis. In the study by Yousry et al (23), the mean serum levels of IL-17 significantly decreased in patients with psoriasis after a three-week treatment with 0.05% betamethasone and 3% salicylic acid ointments twice daily, compared to the baseline level, since this difference was statistically significant. The PASI score also decreased after three weeks, but the difference was not significant compared to the baseline. In the present study, instead of the combination of salicylic acid with betamethasone ointments, fluocinolone cream and betamethasone ointment were applied and the duration of treatment was also four weeks. The inconsistency between the present study and the study by Yousry et al (23), in terms of PASI score may be due to differences in the combination of medications or duration of treatment.

In a clinical trial by Krueger et al (2), a significant decrease was observed in keratinocytes density, epidermal thickness and other symptoms in psoriatic patients following the subcutaneous injection of anti-IL-17 (ixekizumab) and after six weeks, the skin lesions returned to normal. They also concluded, IL-17 may play a key role in the pathogenesis of psoriasis. Likewise, the results of a review study by Chiricozzi and Krueger (24) showed that

IL-17 receptor antagonists play an important role in the treatment of psoriasis patients.

In the studies by Leonardi et al (6) and Nakagawa et al (25), patients with moderate and severe psoriasis received different doses of anti-IL-17 (ixekizumab) and their outcomes were compared with those who received placebo. The results of these studies indicated a minimum of 75% decrease in PASI score with a dose-response relationship. In the present study, administration of fluocinolone cream and betamethasone lotion for one month improved and decreased PASI score in 96.67% of the patients, although the mean reduction in PASI score was 42% in this topical medication.

In contrast to the above-mentioned studies, in the present study, instead of intervening with the IL-17 pathway and using IL-specific inhibitors, topical non-specific treatment with fluocinolone and betamethasone was used which in addition to affecting the severity of psoriasis, reduced serum levels of IL-17.

Conclusion

In the present study, we found, serum levels of IL-17, as a pro-inflammatory cytokine, was higher in patients with psoriasis than healthy controls. Besides, treatment of psoriasis with topical medications reduced serum levels of IL-17 and severity of disease, which reflecting the value of IL-17 as a biomarker in assessment of response to treatment. To investigate whether IL-17 is a causative agent of psoriasis or increases in response to psoriasis, further studies should be conducted to examine the expression of IL-17 in skin lesions along with its serum levels measurement.

To compare the therapeutic effect of topical anti-inflammatory drugs with anti-IL-17 on psoriatic lesions, we suggest a clinical trial be conducted in which patients with psoriasis are divided into three treatment groups that are matched in term of severity according to PASI. In the first group only anti-IL-17, in the second group only topical medications including fluocinolone and betamethasone and in the third group, a combination of anti-IL-17 and topical medications to be administered.

Limitations of the study

This study was done for therapeutic effect of topical anti-inflammatory drugs on serum levels of IL-17. Evaluation of therapeutic effect of systemic anti-inflammatory drugs is limitation of this study.

Authors' contribution

MS and HRGB were the principal investigators of the study. MS, HRGB and FS were included in preparing the concept and design. MS, HRGB, MASR and FS revisited the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The Ethics Committee of Hamadan University of Medical Sciences approved this study (ethical code #IR.UMSHA.REC.1395.62). Accordingly, written informed consent was taken from all participants before any intervention. This study was extracted from M.D., thesis of Fariba Shadfar at this university (Thesis #9503251550). Besides, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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