Short Paper

# Serum Levels of IL-10 and IL-22 Cytokines in Patients with Psoriasis

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## ABSTRACT

**Background**: As a chronic inflammatory condition, psoriasis results from an interaction between genetic and immunologic factors in a predisposing environment. In spite of compelling evidence for the role of T cells and cytokines in psoriasis, interleukin (IL)-10 and IL-22 have not been sufficiently investigated. **Objective:** To assess the serum levels of IL-10 and IL-22 in patients with psoriasis compared to healthy controls. **Methods**: A total of 28 patients with psoriasis were compared with 28 age and sex-matched healthy subjects. Psoriasis Area and Severity Index (PASI) criteria were used to measure the severity of the disease. Serum levels of IL-10 and IL-22 were measured in both groups and compared. **Results**: The mean serum level of IL-10 was 89.5±18.7 in patients compared to 117.2±23.4 pg/ml in the controls (p=0.36). Also, serum level of IL-22 was 284.1±49.7 in patients versus 425.4±82.8 pg/ml in control group (p=0.17). There was a significant direct correlation between levels of IL-10 and IL-22 in patients group (p=0.0005). The clinical severity of psoriasis was significantly correlated with high levels of IL-22 (p<0.0001).**Conclusions**: The decreased levels of IL-10 in psoriatic patients and direct correlation between higher levels of IL-22 and disease severity support the clinical implication of both cytokines in psoriasis.

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**Keywords: IL-10, IL-22, Psoriasis**

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## INTRODUCTION

Psoriasis is a common chronic relapsing disease which may present in plaque, reverse, postular, and erythrodermic forms (1). As a chronic inflammatory condition, psoriasis results from an interaction between genetic and immunologic factors in a predisposing environment (2). Increased immune activity has been proposed as the main cause of psoriasis owing to T-cell aggregation in the skin secreting a variety of inflammatory mediators. Accordingly, these cytokines result in excessive skin regeneration which in turn causes thickened plaques, red patches, scaling, itching and burning sensation (1,3,4).

Interleukin-10 (IL-10) is a member of cytokine family produced by monocytes, Th2 cells, mast cells and some of non-lymphoid cells such as keratinocytes. IL-10 as a pleotropic cytokine plays a major role in inhibiting macrophage activities, T-cell activation, and termination of inflammatory responses (5-7). Elucidation of the low level expression of IL-10 in psoriasis and given the induction of IL-10 expression by conventional anti-psoriatic therapies, this cytokine appears to have important clinical implications in psoriasis (8,9). Furthermore, IL-10 gene polymorphism and gene expression pattern are potentially relevant with pathophysiology of this immune-mediated disease (9).

Another member of IL-10 family is IL-22 which is produced by several sub-populations of lymphocytes particularly Th17, Th1 and Th22 cells. Recent studies have shown increased expression of IL-22 in psoriatic lesions and raised serum levels in these patients compared to healthy subjects (10,11). Due to increasing interest in IL-10 and IL-22 for diagnosis and treatment purposes of psoriasis, our study aimed to measure serum levels of these two cytokines in psoriasis patients and compare it with healthy control subjects.

## MATERIALS AND METHODS

A case-control study was carried out in a University Hospital in Hamedan, Iran enrolling 28 psoriasis patients, 21 males (75.0%) and 7 females (25.0%), attending the dermatology clinic of the hospital between August 2012 and May 2013. Inclusion criteria were diagnosis of psoriasis according to a reliable history findings and physical examination and giving an informed consent approved by our institutional ethics committee to enter this study. Patients with concomitant chronic, inflammatory and autoimmune diseases were excluded from the study. The patients with the history of drug withdrawal for at least 3 months were recruited in this study. A total of 28 age- and sex-matched healthy subjects with no history of chronic, inflammatory or autoimmune diseases were included as control group. Progression or remission of the disease was determined according to the Psoriasis Area and Severity Index (PASI). This index combines the assessment of the severity of lesions as estimated by three clinical signs (Erythema, Induration and desquamation) and the area affected (Head, Arms, Trunk and legs) into a single score ranged from 0.0 to 72.0 so that, patients with PASI <7.5 were diagnosed as mild form, PASI =7.5-12.5 as moderate and PASI >12.5 as severe form of disease (12).

**Cytokines Measurement.**Serum samples were collected form psoriatic patients before starting the drug treatment and from control subjects and were kept in -20 ºC until tested

for cytokine levels. The commercial ELISA kits were used to determine the serum levels of IL-10 (eBioscience, Germany) and IL-22 (eBioscience, Germany) according to the manufacture's protocol.

**Statistical Analyses.** Data analysis was performed using SPSS for windows (Version 19, Chicago Inc, US). Student *t*-test and Mann-Whitney U test were used for quantitative variables and Chi-square test or Fisher's exact test were used for categorical variables. Spearman rank correlation coefficient was applied for correlation analyses. The probability values less than 0.05 was considered as statistically significant.

## RESULTS AND DISCUSSION

A total of 56 subjects were enrolled in this study and compared in two equal patients (N=28) and control (N=28) groups. The mean age of patients group was 46.7±17.4 years versus 44.5±16.8 years in the controls. There was no significant difference between the two groups in terms of age and gender proportions. The average PASI score of severity and duration of disease were 10.02±7.8 and 8.6±12.9 years, respectively. According to the PASI scores, 13 (46.4%) cases had mild form of psoriasis (PASI<7.5), 7 (25.0%) cases had moderate form (PASI=7.5-12.5) and 8 (28.6%) cases had severe form of the disease (PASI>12.5). Distribution of the clinical forms of psoriasis were as follows; 24 (85.7%) cases with plaque psoriasis, 1 (3.6%) with gutate psoriasis and 3 (10.7%) cases with mixed form (Plaque and gutate, Plaque and pustular and gutate and pustular).

The mean serum levels of IL-10 were 89.4±18.68 pg/ml in psoriasis patients and 117.2±23.4 pg/ml in control group (p=0.36, Figure 1).

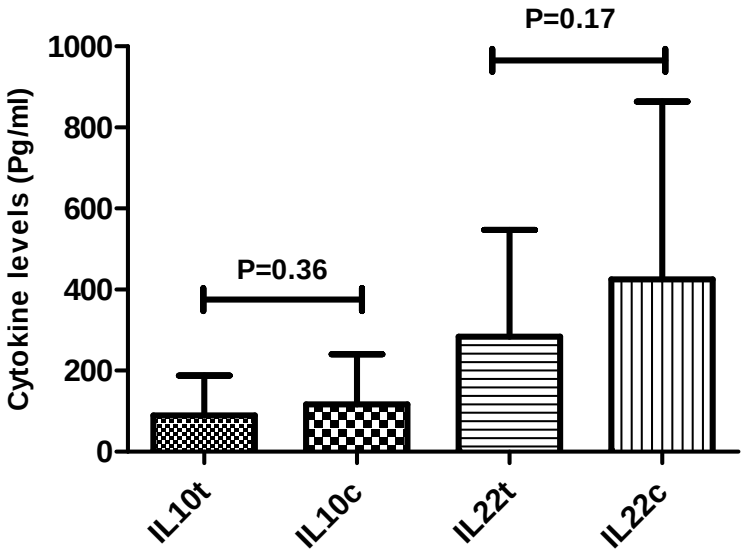


**Figure 1.**Comparison of the cytokines levels between patients and control groups. t: test, c: control.

Also, the mean levels of IL-22 were 284.1±49.7 pg/ml in psoriasis patients versus 425.4±82.8 pg/ml in healthy controls (p=0.17, Figure 1). Spearman rank correlation analyses showed a significant direct correlation between the levels of both cytokines in psoriatic patients (r=0.66, P=0.0005, Figure 2).

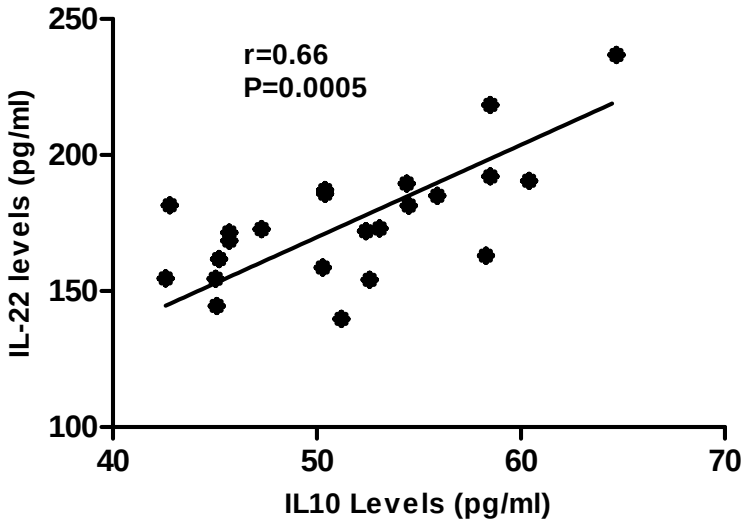


**Figure 2.**Pearson correlation between IL-10 and IL-22 levels in patients group. A significant direct correlation between the decreased levels of both cytokines in psoriatic patients has been shown.

The clinical severity of psoriasis was significantly correlated with increased levels of IL-22 in that group of patients with severe form of disease (r=1.00, p<0.0001). However, the mean levels of IL-10 and IL-22 cytokines were not statistically different between three groups of the patients in terms of the severity of disease (Table 1).

**Table 1: Comparison of the serum cytokines concentrations between the three groups of the patients with mild, moderate and severe forms of the disease.**

| Form of disease | IL-22 Conc (pg/ml) | IL-10 Conc (pg/ml) |
|---|---|---|
| Severe (n=8) | 276.3 ± 1.6 | 73.1 ± 17.3 |
| Moderate (n=7) | 255.5 ± 1.1 | 76.5 ± 16.8 |
| Mild (n=13) | 253.2 ± 1.4 | 82.3 ± 16.1 |
| P Value | 0.63 | 0.58 |

All data presented as Mean ± SEM.

Several studies have documented the effective role of IL-10 in resolution of acute stage of psoriasis and prevention of its recurrence. Hence, administration of IL-10 has been proposed as an effective antipsoriatic treatment. IL-22 is another member of IL-10 family which has an important role in regulation of keratinocyte proliferation and migration, inhibition of kertainocyte differentiation, and induction of pro-inflammatory cytokines as well as chemokines leading to skin thickening (13).

Regarding to the role of IL-10 in psoriasis, few studies demonstrated a significant decreased serum level of IL-10 in psoriatic patients in comparison to healthy controls (14,15). Varghese *et al.,* showed lower but insignificant level of IL-10 in psoriatic patients than controls (16). In line with these findings, we observed low serum levels of IL-10 in our patients group compared to healthy controls although, it was not statistically significant probably due to the small number of patients in the current study. In contrast to our results and other previous reports, Borska *et al*., and Roussaki-Schulz*eet al.,* depicted an increased level of IL-10 in psoriatic patients versus healthy controls. They speculated that this unexpected increase in IL-10 level could be due to therapeutic intervention and counterbalance interaction between pro- and anti-inflammatory cytokines during inflammatory responses (17,18). Altogether, because of the limited number of related studies on psoriasis and reported inconsistent results, further investigations are needed to explore the clinical relevance of regulatory cytokine IL-10 particularly with regard to its therapeutic implications in psoriatic patients. However, genetic polymorphism of IL-10, which may affect the expression of this antipsoriatic cytokines, is another important subject that must be considered for discussing the serum levels of IL-10 in relation to its potentially protective influence in psoriasis. Due to the lack of genetic data in our study, the results should be interpreted cautiously.

Exploring the role of IL-22 in the immunopathogenesis of psoriasis in recent years has revealed that IL-22 could be considered as an essential player in the inflammatory process of psoriasis (19,20). Recent studies on pathogenesis of psoriasis in relation to IL-22, demonstrated an increased level of this cytokine and its direct correlation with severity of disease in psoriatic patients which is indicative for critical role of IL-22 in development of psoriatic lesion. Similar results were also reported by Michalak-Stoma *et al.* suggesting the importance of early assessment of serum biomarkers in psoriatic patients to prevent severe progression of the disease (13). Accordingly, this molecule could be another target for immunotherapeutic intervention in order to control inflammatory response in psoriasis as an autoimmune inflammatory disease (11,21). Although, based on preclinical and few clinical investigations, this cytokine with pleiotropic function has dual pro- and anti-inflammatory nature and hence, therapeutic potential of this molecule is still under debate (22).

In contrast to previous reports (10,11,13), we observed a decreased but insignificant level of IL-22 in psoriatic patients versus healthy controls. Notably, only 8 cases with severe form of disease showed a significant higher level of IL-22 which is in line with above mentioned studies. More recently, an *in vitro* study by Kouris *et al*. (23) showed the increased levels of TNF-α and IL-17 but no change in IL-22 concentrations in the supernatant of stimulated peripheral blood mononuclear cells (PBMCs) from psoriatic patients compared to healthy controls. These discrepancies could stem from the methodological differences such as sampling conditions, therapeutic interventions, various clinical forms of the disease, and other unknown factors between the studies as well as the low number of patients in the current report. Given the emerging role of IL-

22 in autoimmune disease, drawing a clear conclusion for the role of this cytokine in psoriasis by analyzing the limited number of studies seems to be overlooked. Hence, our results should be interpreted with caution and definitely further investigations required to confirm the possibly protective or harmful effects of IL-22 in pathogenesis of psoriasis. Furthermore, local expression analysis of this cytokine along with other pro-inflammatory cytokines inside the psoriatic lesions (e. g. mRNA expression quantification or immunohistochemistry analyses) would be more comprehensive to explain the contribution of these cytokines in immunopathogenesis of psoriasis. In this context, previous reports have clearly showed an association between local mRNA expression of IL-22 and high serum levels of this cytokine in psoriasis patients (11).
Elucidation of direct correlation between decreased levels of IL-10 as an anti-inflammatory cytokine and decreased levels of IL-22 as a pro-inflammatory cytokine could be indicative of complex pathophysiology of psoriasis. Although, variations in genetic factors that regulate the mRNA expression levels or protein expression for both cytokines which have not been tested in the current study as well as history of earlier therapeutic interventions could be the plausible explanations for these results and definitely needs to be confirmed by further well-designed investigations in psoriasis patients. In this regard, better understanding of the function and interaction of both cytokines particularly IL-22 in the context of cytokine network during chronic inflammatory conditions like psoriasis would certainly be helpful in treatment of autoimmune diseases.

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