

## Research Article

# Serum Levels of Selected Th17 and Th22 Cytokines in Psoriatic Patients

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*Introduction.* Psoriasis is a T cell-mediated inflammatory disease in which pathogenesis T helper (Th) lymphocytes (Th1, Th17, and Th22) play an important role. The aim of the study was to assess the serum levels of some cytokines involved in the Th17 and Th22 responses in psoriatic patients. *Material and Methods.* The study comprised 60 psoriatic patients and 30 healthy controls. In the serum collected from psoriatic patients and healthy controls, the concentrations of IL-6, IL-12, IL-17, IL-20, IL-22, and IL-23 were examined with ELISA kits. Severity of psoriatic skin lesions was assessed by means of PASI, BSA, and PGA scores. *Results.* IL-6, IL-20, and IL-22 concentrations were significantly higher in psoriatic patients in comparison with the control group. The positive correlations between the concentrations of IL-22 and IL-20 and severity of psoriasis assessed with PASI and BSA scores as well as IL-17 and PASI score were found. There was also a positive correlation between IL-23 and IL-17 concentrations. *Conclusions.* Results of the conducted studies suggest that Th22 response may contribute to the skin and systemic inflammatory disease in psoriasis. It seems that early identification of soluble biomarkers and initiation of well-matched treatment may prevent exacerbation and progression of psoriasis.

## 1. Introduction

The knowledge about the role of cytokines in psoriasis has developed in the last several years. Initially, only Th1 cells and cytokines secreted by these cells, like TNF- $\alpha$ , IFN- $\gamma$ , and IL-2, have been associated with the development and maintenance of chronic inflammatory diseases, such as psoriasis. Th1 cells differentiate from naive CD4+ cells in the presence of IL-12, IL-18, and IFN $\alpha$  and  $\gamma$ . It is well known that Th1 cytokines have strong inflammatory effects in activating macrophage, neutrophil, and CD8+ cytotoxic T cells [1].

In the 1990s, Th17 cells were described as a new T-cell population that produces IL-17, IL-6, IL-21, IL-22, and TNF [2]. Transforming growth factor (TGF)- $\beta$ 1, IL-6, IL-23, and IL-15 stimulated initial Th17 differentiation from naive T cells [3]. TGF- $\beta$ 1 is secreted by activated T cells and it initiates T cell and fibroblast activation, as well as angiogenesis and neovascularization [3–7]. IL-6, secreted by macrophages,

endothelial cells, and epithelial cells, is responsible for augmentation of keratinocyte hyperplasia and invasion of macrophages and T cells [3, 8]. IL-15, produced by monocytes, macrophages, DCs, and T cells, can appear to induce angiogenesis, immune cell recruitment, and activation of keratinocytes [4, 9, 10]. Once the Th17 phenotype is achieved, IL-23 maintains a cellular Th17-polarisation [11]. Cytokines produced by Th17 cells were found to initiate acanthosis, hyperkeratosis, and parakeratosis. Th17 cells demonstrated involvement in neutrophil and monocyte chemotaxis, T-cell migration and activation, and neovascularization [3].

Th22 cells have been recently described as inflammatory CD4+ T cells that produce cytokines such as IL-22, IL-26, and IL-13 of which IL-22 is the most important functional cytokine. Th22 cells do not express IL-17A or IFN- $\gamma$  [12–15]. Recent studies indicate that IL-6 and TNF- $\alpha$ , along with the help of plasmacytoid dendritic cells, can promote the Th22 phenotype [14, 16].

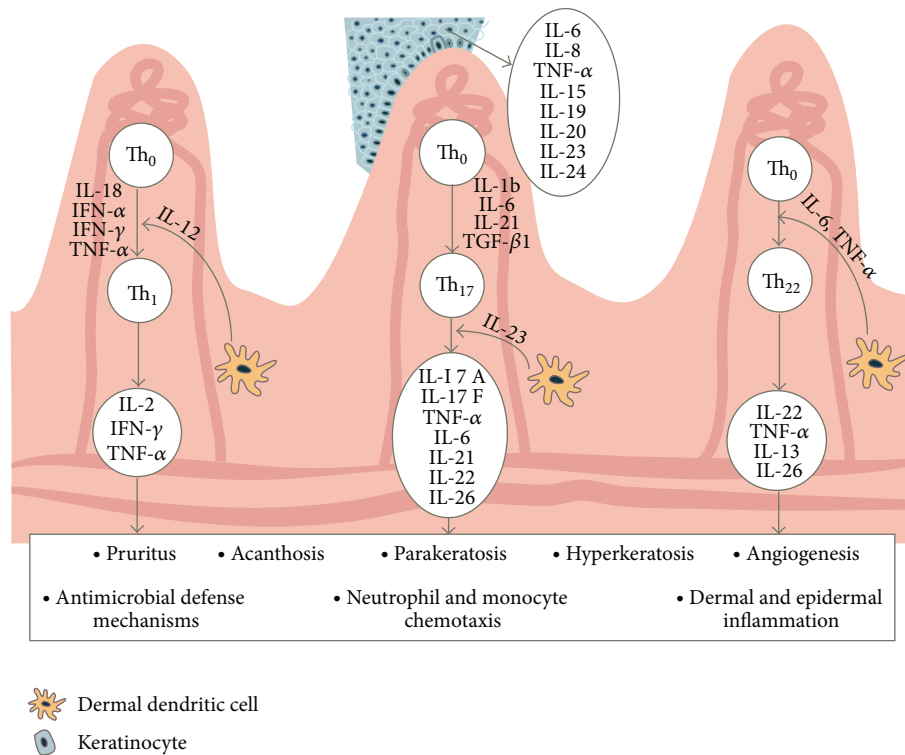


FIGURE 1: Th1, Th17, and Th22 cytokines in the pathogenesis of psoriasis.

IL-20 resembles IL-22 structurally and belongs to the same cytokine family. IL-22 can stimulate IL-20 production in keratinocytes [15].

The differentiation of main three T cell subsets involved in the pathogenesis of psoriasis, as well as Th1, Th17, and Th22 cytokine production are illustrated in Figure 1.

The aim of the study was to assess the serum levels of some cytokines involved in the Th17 and Th22 responses in psoriatic patients.

## 2. Materials and Methods

**2.1. Characteristics of the Studied Group.** The study comprised 60 psoriatic patients, 50 males (83.33%) and 10 females (16.67%), as well as 30 healthy controls. The studied patients' age was between 18 and 69 years,  $45.6 \pm 13.2$  years on average. The history of the disease was from 1 to 45 years,  $18.7 \pm 11.5$  years on average. Thirty-seven patients (61.67%) suffered from persistent psoriatic skin lesions. Thirty-four of the studied patients (40%) reported two psoriasis exacerbations a year, whereas 9 persons (15%) observed as many as 4 exacerbations a year.

**2.2. Assessment of Psoriasis Severity.** The skin lesions severity was assessed with the use of Psoriasis Area and Severity Index (PASI), Body Surface Area (BSA), and Physician Global Assessment (PGA) scores. The PASI value in the studied group was from 4.8 to 64.2 and  $15.7 \pm 9.7$  on average. The BSA value was in the range of 9.0–96.9% and  $31.4 \pm 18.2$  on

average. The PGA score was 3 in 24 individuals (40%), 4 in another 24 individuals (40%), and 5 in 12 individuals (20%).

**2.3. Assessment of Cytokine Serum Concentrations in the Psoriatic Patients and the Controls.** Blood samples were collected from psoriatic patients and controls and were centrifuged for 15 minutes at  $1000 \times g$ . Then, serum samples were subdivided into small aliquots to be stored at  $-80^\circ\text{C}$  until tested for cytokine levels. ELISA kits were used to determine IL-6, IL-12, IL-17, IL-20, IL-22, and IL-23 (R&D Systems, Minneapolis, MN, USA) serum levels, according to the manufacturer's instructions.

**2.4. Statistical Analyses.** Statistical analyses were performed using STATISTICA software. Continuous variables were presented as mean  $\pm$  standard deviation, while categorical variables were presented as absolute and relative frequencies. Mann-Whitney's *U* test was used to compare continuous data between the studied and control groups. Pearson's correlation coefficient was used in correlation analyses. 0.05 significant level was assumed in statistical tests.

## 3. Results and Discussion

**3.1. Comparison of the Selected Cytokine Serum Concentrations in the Psoriatic Patients and the Control Group.** The statistical analyses of the conducted study results revealed significantly higher serum levels of IL-6, IL-20, and IL-23 in psoriatic patients comparing to healthy controls (Table 1 and Figure 2).

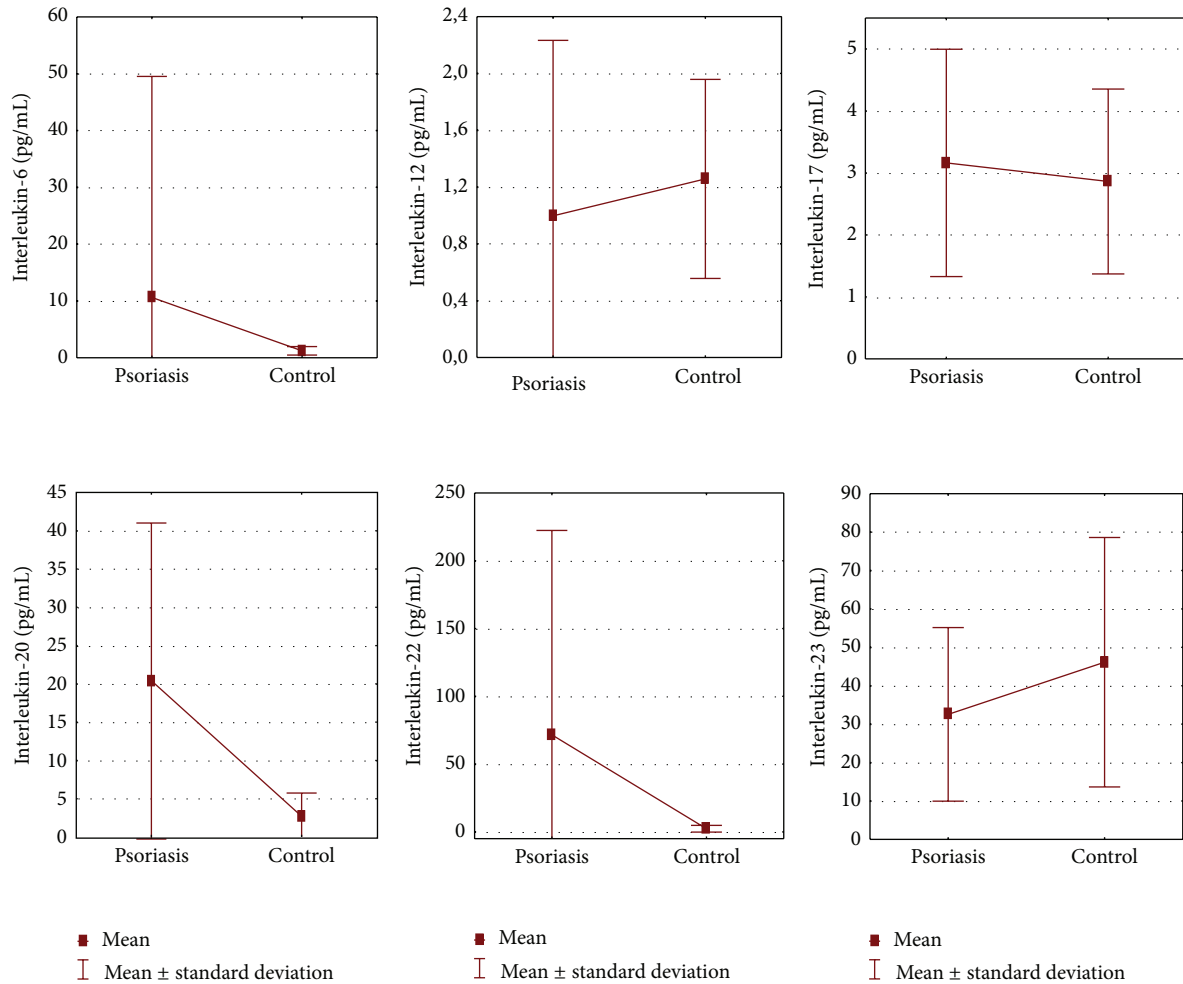


FIGURE 2: Comparing of selected cytokine serum concentrations in the psoriatic patients and the control group.

Significant correlations between IL-20, IL-22, IL-17, and psoriasis severity were observed. No significant correlations were found between the concentrations of the studied cytokines and the sex, age, or psoriasis duration in the studied patients ( $P > 0.05$ ).

**3.1.1. Interleukin-6 (IL-6).** Significantly higher IL-6 values were found in the psoriatic patients in comparison to the control group ( $P < 0.001$ ).

IL-6 contributes to the Th17 cell line’s involvement in numerous processes of inflammation and autoimmunity by preventing the proliferation of T regulatory cells [3]. IL-17 can induce fibroblasts to produce IL-6 potentially activating a positive feedback loop that strengthens Th17 inflammation [12].

Elevated serum IL-6 was observed in psoriatic patients in many studies [17–23]. Dowlatshahi et al. analyzed 78 studies comparing the serum inflammatory markers, including IL-6, in psoriasis with healthy controls [21]. The study showed that the standardized mean differences were higher in psoriatic patients compared to healthy controls for IL-6. Elevated

serum IL-6 appears to be associated with greater psoriasis severity [18, 21, 24]. It was shown that IL-6 might be the biomarker differentiating psoriasis arthritis from psoriasis without joint involvement [19, 22].

**3.1.2. Interleukin-20 (IL-20).** Significantly higher IL-20 values were found in the psoriatic patients in comparison to the control group ( $P < 0.001$ ). A significant positive correlation between the IL-20 concentrations and psoriasis severity measured by the PASI was detected ( $P < 0.001$ ;  $r = 0.698$ ).

IL-20 is produced by keratinocytes in the presence of IL-22, TNF- $\alpha$ , and IL-17 but not IFN- $\gamma$  or IL-20 itself [15, 25]. It can also be produced by stimulated monocytes and DCs [26–28]. IL-20 can play an important role in the later effector phase of psoriasis pathogenesis, in which it inhibits the terminal differentiation, increases antimicrobial competence, and production of chemokines for neutrophils in keratinocytes [25, 29].

There are not many studies concerning IL-20 serum level, but increased levels of IL-20 were noted in lesional skin as

TABLE 1: The selected cytokine serum concentrations in the psoriatic patients and the control group.

Cytokine	Psoriasis	Control	P
IL-6 (pg/mL)	10.622 ± 38.906	1.226 ± 0.745	<0.001
IL-12 (pg/mL)	0.997 ± 1.236	1.257 ± 0.701	0.075
IL-17 (pg/mL)	3.163 ± 1.834	2.863 ± 1.492	0.684
IL-20 (pg/mL)	20.418 ± 20.587	2.703 ± 3.043	<0.001
IL-22 (pg/mL)	71.600 ± 150.759	2.358 ± 2.486	<0.001
IL-23 (pg/mL)	32.553 ± 22.599	46.130 ± 32.476	0.094

well as in the blood in psoriatic patients [25]. As in our study, IL-20 serum levels correlated with PASI scores [25].

**3.1.3. Interleukin-22 (IL-22).** A significantly higher increase in IL-22 was observed in psoriatic patients in comparison with the healthy controls ( $P < 0.001$ ). A significant positive correlation was found between the IL-22 concentration and psoriasis severity measured by both the PASI and BSA score; that is,  $P < 0.001$ ;  $r = 0.557$  and  $P < 0.001$ ;  $r = 0.559$ , respectively.

IL-22 is a member of the IL-10 cytokines family and is mainly produced by Th17, Th22, and mucosal NK cells [30–32]. IL-22 upregulates keratinocyte proliferation and migration, inhibits keratinocyte differentiation by downregulating a variety of genes as filaggrin and involucrin genes [33, 34], and augments the expression of inflammatory molecules by keratinocytes, which leads to an increase in skin thickness *in vitro* and *in vivo* [35–37]. IL-22 increased the expression of the hBD-2 and hBD-3 in human keratinocytes and MMP1 and MMP3 in the skin [38–40].

In psoriasis, IL-22 is overexpressed most probably as a result of upregulated IL-23 and IL-6 levels [12, 41, 42]. IL-22 levels in plasma correlated with psoriasis severity [31]. The treatment with TNF inhibitor (etanercept) reduced serum levels of IL-17 and IL-22 [43].

**3.1.4. Interleukin-12 (IL-12) and Interleukin-23 (IL-23).** No significant differences were found in the IL-12 and IL-23 concentrations between the psoriatic patients and control group ( $P > 0.05$ ).

IL-23 together with IL-12 belongs to the IL-12 family and are both structurally related; IL-12 is formed by the p40 and p35 subunits; IL-23 consists of p40 and p19 subunits [44, 45].

Although both IL-12 and IL-23 are present in psoriasis, studies support that IL-23, rather than IL-12, is crucial during the pathogenesis of psoriasis. IL-23 is overexpressed in psoriasis lesional skin, as shown for example, by increased p40 and p19 mRNA levels but not always p35 [46–54]. IL-23 is overproduced by dermal dendritic cells [48, 53] and keratinocytes [51] in lesional psoriatic skin.

IL-23 has the influence on sustenance and amplification of the chronic inflammation in psoriasis [55]. IL-23 level decreases after psoriasis therapy [51]. On the other hand, most recent reports show no increased expression of the IL-12 in psoriasis [3, 49, 52, 53]. Statistically significant differences in serum IL-12 level have been found in psoriatic patients comparing to healthy controls [20, 56]. However, there are

no significant studies comparing the serum levels of IL-23 in psoriatic patients and controls.

**3.1.5. Interleukin-17 (IL-17).** No significant differences were found in the serum IL-17 concentrations between the psoriatic patients and control group ( $P > 0.05$ ). A significant positive correlation between the IL-17 concentrations and psoriasis severity measured by the PASI was detected ( $P < 0.05$ ;  $r = 0.277$ ).

IL-17 (IL-17A) is a member of a newly identified cytokine family comprising IL-17A, IL-17B, IL-17C, IL-17D, IL-17E (IL-25), and IL-17F. IL-17 and IL-17F have a proinflammatory activity inducing the expression of proinflammatory cytokines, colony-stimulating factors, and chemokines from dendritic cells, neutrophils, T cells, monocyte/macrophages, and epithelial cells [11, 44]. IL-17A and IL-17F can mobilize, recruit, and activate neutrophils [44, 57].

IL-17 is undetectable in normal skin, and biological therapy that inhibits Th17 pathways results in reduced expression of IL-17 and IL-23 and improved disease outcomes [11, 24, 39]. Th17 cells and the cytokines produced by these cells are found in increased levels within skin affected by psoriasis [31, 47–49, 58–60]. Statistically significant differences in serum IL-17A level have been found in psoriatic patients comparing to healthy controls [20]. IL-17 serum levels correlated with the psoriasis area and severity index (PASI) [20].

**3.2. Analysis of Correlations between the Determined Cytokine Concentrations in Psoriatic Patients.** In addition, an analysis of mutual correlations between the concentrations of selected cytokines in the psoriatic patients was conducted. A significant positive correlation between the IL-23 and IL-17 values was found ( $P < 0.05$ ;  $r = 0.271$ ). An increase in the IL-23 concentration was accompanied by an increase in the IL-17 concentration. In previous studies, it was found that interaction of IL-23 with its receptor on Th17 cells stimulates the production of IL-17 and other related proinflammatory cytokines activates NK cells and regulates antibody production [1, 3, 44].

## 4. Conclusions

We believe that the results of our study confirm involvement of Th17 and Th22 cytokines in psoriasis pathogenesis. Elevated IL-22 level without increase of IL-17 level may suggest that Th22 role is more significant in the inflammatory process of psoriasis. Very high concentrations of IL-22 in the patients'

serum can be connected with intensive IL-6 stimulation. IL-22 and IL-20 itself induce production of IL-20, which is elevated in our study. It seems that IL-6, which initiates Th17 and Th22 pathways in psoriasis, may be helpful in the clinical practice as a soluble biomarker of the disease activity and its prognosis. The development of new therapeutical strategies targeting the initial step of cytokine network activation, for example, IL-6, may reduce the next events of inflammatory reactions and prevent the psoriasis exacerbation and systemic complications. Furthermore, serum levels of IL-20, IL-22, and IL-17, which correlated with the clinical severity and activity of psoriasis, may be objective parameters of successful treatment and may be used in the followup.

## Abbreviations

BSA:	Body Surface Area
ELISA:	Enzyme-linked immunosorbent assay
hBD:	Human beta-defensin
IFN:	Interferon
IL:	Interleukin
MMP:	Matrix metalloproteinase
mRNA:	Messenger ribonucleic acid
NK:	Natural killer
PASI:	Psoriasis Area and Severity Index
PGA:	Physician Global Assessment
TGF:	Transforming growth factor
Th:	T helper
TNF:	Tumor necrosis factor.

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