# Relevance of Serum Vascular Endothelial Growth Factor (VEGF) and Serum Interleukin-10 in the Severity of Psoriasis in South Indian Patients: A Case–Control Study

**Deena Patil, Tharayil Kunneth Sumathy, Arakali Lakshminarayana Shyamprasad**
Department of Dermatology, M S Ramaiah Medical College, Bengaluru, Karnataka, India



## Abstract

**Background:** Psoriasis is a chronic inflammatory disorder and is associated with obesity, diabetes mellitus, and hypertension. There is an increased expression of inflammatory cytokines (interleukin [IL]-17, tumor necrosis factor [TNF]-α, IL-22, vascular endothelial growth factor [VEGF]) in the serum of psoriasis patients. Serum levels of IL-10, another anti-inflammatory cytokine, have been found at varying values in psoriasis in different regions of the world. **Aims and Objectives:** The aim of this article is to assess the serum IL-10 and serum VEGF in psoriasis patients with no co-morbidities and healthy controls. **Materials and Methods:** This study was conducted on 46 serum samples (23 psoriasis subjects and 23 healthy controls). After informed consent, 3 mL of serum was obtained and stored at -70°C. The samples were quantitatively assessed for VEGF-A and IL-10 by the enzyme-linked immunosorbent assay. **Results:** This study revealed that the mean (±SD) value of serum VEGF in cases was significantly higher than that in controls (cases = 235.21 ± 138.71; controls = 104.73 ± 36.01 pg/mL). However, levels of serum IL-10, although increased in cases (2.37 ± 1.61 pg/mL) when compared with controls (1.64 ± 0.89 pg/mL), showed no statistical significance. **Conclusion:** In this study, serum VEGF and IL-10 levels were increased in psoriasis when compared with controls but were not significantly related to the Psoriasis Area and Severity Index. The significant correlation between serum VEGF and IL-10 levels in cases when compared with controls suggests their role in the pathogenesis of psoriasis. Persistently increased values in psoriasis patients may lead to the development of comorbidities.

**Keywords:** Interleukin-10, PASI, psoriasis, vascular endothelial growth factor

## Introduction

Psoriasis is a chronic inflammatory disorder which is extremely polymorphic, varying from small nail pits to full blown erythroderma. It is a complex interplay among genetics, immunology, and multiple environmental factors.[1] Globally, the prevalence of psoriasis varies from 0.14% to 1.99%.[2] In India (2010), the prevalence of psoriasis varies from 0.44% to 2.8%.[3] According to the recent data, the countries with the highest number of adults affected with psoriasis were the USA (3.4 million) and India (2.9 million). Psoriasis is now considered a systemic disease with psychological, metabolic, musculoskeletal, and cardiovascular comorbidities.[2] The clinical hallmark of psoriasis, characterized by erythematous scaly plaques, is due to neovascularization in the dermal papillae and psoriasiform hyperplasia of the epidermis.[4] Neoangiogenesis plays an integral role in the immunopathogenesis of psoriasis, with keratinocytes being the source of vascular endothelial growth factor (VEGF).[5,6] Apart from neovascularization, it is known to be involved in epidermal hyperproliferation, leucocyte infiltration in the skin, and also koebnerization in psoriasis.[6,7] With the increased understanding of inflammation in psoriasis, cytokines have been found to play a critical role in its pathogenesis. Psoriatic plaques

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**Address for correspondence:** Dr. Deena Patil, Department of Dermatology, M S Ramaiah Medical College, New BEL Road, Mathikere, Bengaluru 560054, Karnataka, India.
E-mail: deenajc22@yahoo.com



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have been shown to contain increased levels of cytokines, including tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), IL-1a, IL-17, and IL-22.[8,9,10] IL-10 is a pluripotent cytokine and exhibits anti-psoriatic activity on different cell populations including antigen-presenting cells and T-cells.[9,10] Further, regulatory B cells produce IL-10, which ameliorate psoriasis.[11] IL-10 is also produced by keratinocytes upon exposure to UV radiation, exhibiting an immunosuppressive effect.[12] There have been many studies conducted in different parts of the world on the serum values of IL-10 in psoriasis, which have thrown up varying findings.[8] Apart from psoriasis, these cytokines are also known to play a role in diabetes mellitus and hypertension.[13-15] The various clinical types of psoriasis and its severity are dependent on the interaction of the cytokines and keratinocytes.[4,11] The Psoriasis Area and Severity Index (PASI) is a clinical tool to assess the severity of psoriasis.[16] It has its own limitations, being subjective and with a poor sensitivity to changes in small areas of involvement with the disease.[8,16] In the present study, an effort has been made to study the relevance of serum VEGF and IL-10 in psoriasis patients with no comorbidities, to delineate the behavior of these cytokines in psoriasis.

## Materials and Methods

This was a prospective case–control study conducted in the Department of Dermatology of a tertiary care center in South India. This study was conducted during the period from June 2016 to May 2018 after approval from the Institutional Ethics Committee (EC/DRP/10/05-04-2016). A written informed consent was taken from all the participants recruited for the study.

### Study participants

All adult patients (>18 years) with chronic plaque psoriasis with PASI >10 were recruited for the study. These cases were selected after ruling out that they had no comorbidities such as diabetes mellitus or hypertension (confounding factors) and were not on any systemic treatment such as methotrexate, cyclosporine, or phototherapy. Patients who had stopped systemic treatment for a period of 4 months or more at the time of recruitment were also included for the study. Appropriate informed consent was taken from the participants. Patients with psoriatic arthritis and pustular psoriasis were excluded from the study. A detailed history and examination with assessment of severity with PASI score[16] was done for all recruited patients. Routine investigations such as complete blood picture, urine routine, HbA1c (glycosylated hemoglobin), liver function tests, serum creatinine, blood urea, C-reactive protein, chest X-ray, and skin biopsy (in doubtful cases) were done.

### Controls

Age- and sex-matched, otherwise healthy subjects who visited Dermatology OPD for the treatment of non-inflammatory dermatoses were recruited for the study after obtaining informed consent. These individuals were also selected after exclusion of comorbidities such as diabetes mellitus or hypertension.

### Estimation of serum VEGF and IL-10 by ELISA

An aliquot of 3 mL of peripheral blood serum was collected from all the 23 cases and 23 controls and stored in a refrigerator at -70°C until analysis. Repeated thawing and freezing of samples were avoided. Thus, a total of 46 serum samples were taken for the analysis of serum VEGF and IL-10 levels. Commercially available Human VEGF-A enzyme-linked immunosorbent assay (ELISA) kit (Diaclone, France) and Human IL-10 ELISA kit (Diaclone, France) were used for the quantitative estimation of serum VEGF and IL-10 levels, respectively. The stored serum samples were diluted and measured in duplicate. The reaction was terminated by adding sulfuric acid and the absorbance was measured at 450 nm using a spectrophotometer. The absorbance measured in each well by the ELISA reader was proportional to the concentration of the respective cytokines present in the serum sample.

### Statistical analysis

In this study, descriptive statistics comprising mean ± SD were computed for age, body mass index (BMI), PASI score, and cytokine levels. The independent *t*-test was used to compare mean±SD of cytokines levels between cases and controls. Pearson's correlation coefficient was used to assess the correlation between age and cytokine levels and other factors. The level of significance was fixed at $P < 0.05$. The statistical analysis was done using SPSS version 16 software.

## Results

On analyzing the results, of the 46 subjects, 23 were cases with moderate-to-severe psoriasis and 23 were age- and sex-matched subjects without psoriasis or any other chronic inflammatory diseases. The mean age of cases and controls was found to be 37.96 years (SD ±11.92) and 38.48 years (SD±12.32), respectively, thus being matched for age and sex. Similarly, the mean of BMI in the cases and controls was 25.3 (±7.67) and 24.7 (±2.87), respectively. The difference in BMI was not statistically significant ($P = 0.774$). Among the cases, 43.47% (10 cases) had BMI ranging from 21 to 30, whereas in healthy controls it was 91.3% (21 controls). In the cases, the mean duration of the disease was 10.17 (±6.7) years. The mean PASI score was 27.54 (±10.48) with 61.5% (8 cases) having score ranging from 10 to 20, followed by 53.8% (7 cases) having PASI score ranging from 31 to 40 [Table 1].

Comparisons of the two groups revealed a significantly higher mean value of VEGF ($P = 0.001$) in cases, whereas the difference in the mean value of serum IL-10 ($P = 0.095$)

**Table 1: Demographic and clinical characteristics of cases and controls**

| | Cases ($n$=23) | Controls ($n$=23) |
|---|---|---|
| Age (mean±SD, years) | 37.96 (±11.92) | 38.48 (±12.32) |
| Male | 12 | 12 |
| Female | 11 | 11 |
| BMI (mean±SD, kg/m$^2$) | 25.26 (±7.67) | 24.70 (±2.87) |
| 10–20 | 7 | 1 |
| 21–30 | 10 | 21 |
| 31–40 | 5 | 1 |
| >41 | 1 | 0 |
| Waist circumference (mean±SD), cm | 87.5 (±19.5) | 88.5 (±14.2) |
| Duration of disease (mean±SD), years | 10.17 (±6.7) | — |
| PASI score | 27.54 (±10.28) | — |
| 10–20 | 8 | — |
| 21–30 | 5 | — |
| 31–40 | 7 | — |
| >41 | 3 | — |

*SD = standard deviation, BMI = body mass index, PASI = Psoriasis Area and Severity Index

**Table 2: Cytokines levels in cases and controls**

| Cytokines | Cases (mean±SD), pg/mL | Controls (mean±SD), pg/mL | $P$-value |
|---|---|---|---|
| VEGF | 235.21±138.71 | 104.73±36.01 | 0.001* |
| IL-10 | 2.37±1.61 | 1.64±0.89 | 0.095 |

**Table 3: Correlation coefficient for serum VEGF and IL-10 among cases and controls**

| | Serum VEGF | $P$-value | Serum IL-10 | $P$-value |
|---|---|---|---|---|
| Age ($n$=46) | -0.004 | 0.981 | -0.247 | 0.098 |
| Duration of the disease ($n$=23) | 0.089 | 0.687 | -0.096 | 0.664 |
| BMI | | | | |
| Cases ($n$=23) | 0.373 | 0.080 | 0.103 | 0.641 |
| Controls ($n$=23) | -0.267 | 0.219 | -0.079 | 0.719 |
| Waist circumference | | | | |
| Cases ($n$=23) | 0.036 | 0.872 | -0.037 | 0.866 |
| Controls ($n$=23) | -0.354 | 0.098 | -0.297 | 0.169 |
| PASI score ($n$=23) | 0.272 | 0.209 | 0.071 | 0.748 |
| C-reactive protein ($n$=23) | 0.104 | 0.636 | 0.303 | 0.160 |
| HbA1c ($n$=23) | 0.226 | 0.299 | 0.006 | 0.978 |

BMI = body mass index, PASI = Psoriasis Area and Severity Index, HbA1c = glycosylated hemoglobulin

was not statistically significant [Table 2]. Pearson's correlation of the serum VEGF and IL-10 with age, PASI, BMI, C-reactive protein, and glycosylated Hb was not statistically significant [Table 3]. Pearson's correlation between VEGF and IL-10 showed statistical significance in cases ($P$ = 0.05) but not in controls ($P$ = 0.37).

## Discussion

Psoriasis is a chronic inflammatory papulosquamous disease, wherein there is involvement of an array of cytokines and growth factors. This inflammatory process continuing for a prolonged duration, along with environmental factors, results in various systemic diseases such as diabetes mellitus, hypertension, dyslipidemia, and inflammatory bowel disease.[1,17]

In our study, we evaluated serum VEGF and IL-10 levels in psoriasis patients and healthy controls. Serum VEGF is secreted by keratinocytes upon stimulation of epidermal cells by upregulated Th-1 cytokines.[6] A metanalysis done by Zafar *et al.*[13] found that the serum VEGF level is also elevated in diabetic and hypertensive patients who did not have psoriasis. Thus, serum VEGF is likely to be involved in the pathogenesis of psoriasis, diabetes mellitus, and hypertension. Hence, these confounding factors (diabetes mellitus and hypertension) were eliminated in our study.

A study done by Nofal *et al.*[18] showed a positive significant correlation between serum VEGF levels in psoriasis and controls. Andrys *et al.*[5] conducted a study on serum VEGF in psoriasis, which showed increased levels in psoriasis patients compared with healthy

controls, with its levels post treatment also significantly increased. Flisiak *et al.*[19] also found an increased VEGF level after treatment in psoriasis patients when compared with controls. In our study, VEGF levels in psoriasis patients with no comorbidities were significantly increased when compared with controls. The correlation between serum VEGF and other parameters was also studied. In our study, the correlation between serum VEGF value and BMI was higher in cases ($P$ = 0.08) when compared with controls ($P$ = 0.22). Silha *et al.*[20] conducted a study on 58 healthy subjects with differing BMIs, which showed a significant correlation with serum VEGF ($P$ = 0.04). There was no significant correlation between serum VEGF and HbA1c and waist circumference in our patients. Nofal *et al.*[18] also showed a positive significant correlation between high serum VEGF levels and severity of psoriasis. However, in the present study, the correlation between serum VEGF and PASI score was not statistically significant [Figure 1]. This lack of correlation in our study could be because of lower number of patients or a different demographic and ethnic profile. Our results of a high serum VEGF in psoriasis patients suggest a possible role for this factor in angiogenesis occurring in psoriasis. Its increased levels may also be a pointer to the development of metabolic syndrome in psoriasis.[13] However, even though the levels of VEGF are high in psoriasis patients, we did not find it to correlate with the severity of psoriasis.

Serum IL-10 is secreted by keratinocytes and regulatory B-cells, imparting anti-inflammatory action in psoriasis.[6,12] It is seen that there is upregulation of IL-10 receptors on keratinocytes on exposure to ultraviolent B-light.[12] In a study done by Khandpur *et al.*[21] on Th-1 and Th-2 cytokines, it was shown that there was significantly raised IL-10 in both active and stable psoriasis patients. Borska *et al.*[22] conducted a study on 55 psoriasis patients in which they found that IL-10 was significantly high in patients compared with controls. In a study conducted in the northern part of India by Verghese *et al.*,[23] it was found that although IL-10 levels were higher in controls than in cases, it was not statistically significant. In our study, serum levels of IL-10 were increased compared with controls but not in statistically significant numbers. In contrast, other studies have shown either a decrease in or undetectable levels of IL-10, compared with healthy controls.[24-26] Our study, however, did not show any correlation of IL-10 levels with severity of psoriasis as defined by PASI ($P$ = 0.74) [Figure 2]. It is interesting to note that in a study conducted in north India, IL-10 showed a positive correlation with PASI, whereas other cytokines such as IL-2, IL-4, and interferon-γ did not show any correlation with PASI.[19]

In a study correlating serum IL-10 and BMI, conducted on 268 individuals by Nematollahi *et al.*,[15] it was shown that detectable values of IL-10 were seen in individuals with lower BMI. In our study, however, there was no significant correlation between serum IL-10 and BMI in cases ($P$ = 0.64) as well as in controls ($P$ = 0.71).

We assume from our findings that serum IL-10 may have a probable role in psoriasis. There is no significant correlation in the values between psoriasis cases and controls with respect to IL-10 in most of the Indian studies. Because of its anti-inflammatory properties, IL-10 could possibly be used in the treatment of psoriasis.

In our study, there was a significant correlation between VEGF and IL-10 in cases when compared with controls. There are no comparative studies regarding VEGF and IL-10 correlation in psoriasis. On comparing serum VEGF and IL-10 values in cases and controls, it was found that VEGF was a significantly better inflammatory marker in cases.

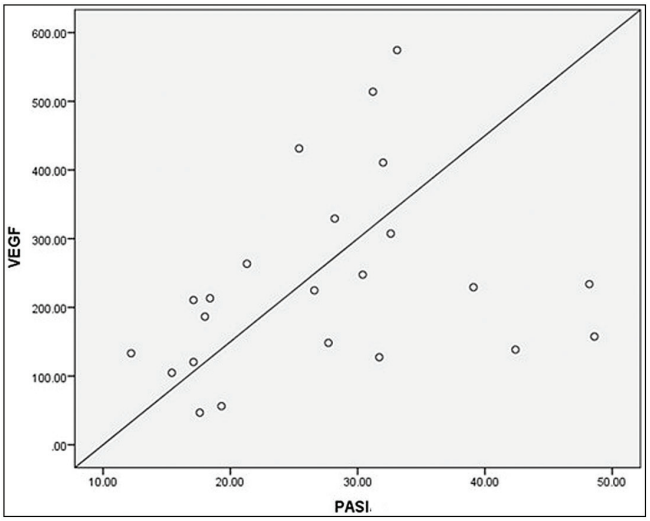


**Figure 1:** Correlation between PASI score and serum VEGF without systemic treatment

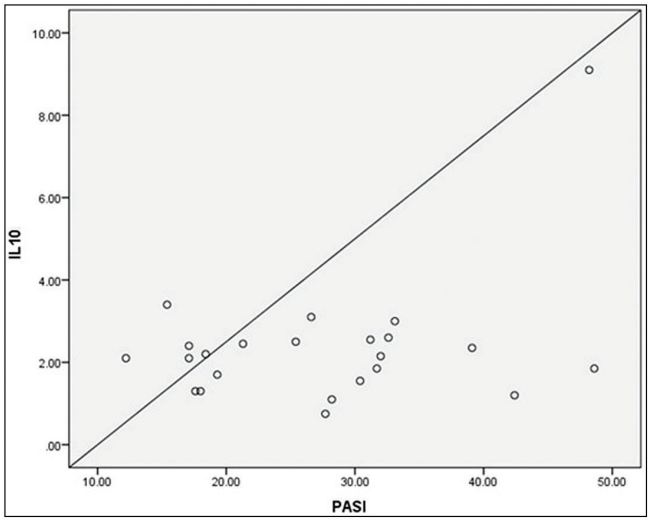


**Figure 2:** Correlation between PASI score and serum IL-10 without systemic treatment

## Limitations of the study

Our study is limited by a small sample size. The small sample size is due to the study being conducted in a single center and because of excluding cases and controls with comorbidities such as hypertension and diabetes mellitus.

## Conclusion

Our study was on serum VEGF and IL-10 levels in psoriasis patients with no comorbidities. We conclude that there is a probable role of VEGF and IL-10 in psoriasis as their values show significant correlation in cases when compared with controls. There is a need for further studies on VEGF and IL-10 levels in psoriasis patients pre- and post-treatment. Our study is probably unique as we have studied psoriasis patients with no comorbidities. The increased levels of VEGF and IL-10 even in these cases suggest that inflammation occurs early in psoriasis much before the development of metabolic syndrome. This may help in delineating the role of VEGF and IL-10 in psoriasis.

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## Declaration of patient consent

The authors certify that they have obtained appropriate informed written consent from the patients and controls. Patients and controls have also given their consent for publication.

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## Conflicts of interest

The authors declare that there are no conflicts of interest.

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