ORIGINAL ARTICLE

# ZFP36 and IL6 expression in Plaque Psoriasis: A clinical and Immunohistochemical Study

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Abstract

*Objectives:* ***ZFP36, a key post-transcriptional regulator, and IL-6, a proinflammatory cytokine, play significant roles in psoriasis pathogenesis.***

*Aim:* ***This study will examine their IHC expression in perilesional and lesional psoriatic skin in contrast to controls.***

*Methods:* ***This study included thirty healthy controls and thirty patients with plaque psoriasis. Clinical data was obtained. Histopathological analysis together with ZFP36 and IL-6 IHC technique were performed.***

*Results:* ***ZFP36 was 100% positive in the epidermis of the control group, with an average positive cell percentage of 84.6±12.1, while in the dermis, positivity was 70% with a mean count of 7.28±5.58/10HPF. In psoriatic lesional skin, epidermal ZFP36 positivity was 80% with a reduced mean positive cell percentage (31.4±19.1), while dermal ZFP36 was observed in 73.3% with a mean count of 35.8±29.2/10HPF. A significant decrease in epidermal ZFP36 positivity, percentage, and H-score was observed across the groups (P = 0.04, 0.001, and 0.001, respectively), while dermal ZFP36 was highest in lesional skin (P = 0.001). For IL-6, epidermal expression was highest in the control group (100%, 65.3±30.8 positive cells) and significantly decreased in psoriatic lesional skin (40%, 28.7±27.3, P = 0.001). Dermal IL-6 was negative in controls but increased dramatically in psoriatic lesional and prelesional skin (P = 0.001). There was a negative connection between dermal ZFP36 and epidermal IL6 (P = 0.03).***

*Conclusion:* ***Our findings suggest that ZFP36 downregulation may contribute to chronic inflammation in psoriasis. The inverse correlation between epidermal IL-6 and dermal ZFP36 expression patterns may indicate their differential regulatory mechanisms in psoriasis pathogenesis.***

*Keywords:* Plaque psoriasis; ZFP36; IL6; Immunostaining; Target therapy

## 1. Introduction

An immune-mediated chronic inflammatory hyperproliferative illness with a hereditary basis, psoriasis is typified by epidermal hyperplasia with abnormal keratinocyte differentiation, dermal angiogenesis, and mixed leucocytic infiltration in both dermis and epidermis. It is one of the most prevalent chronic inflammatory skin disorders in the world, which lowers the quality of life for those who have it.[1]

Psoriasis affects 2% of people worldwide, but 4.6% and 4.7% of people in America and Canada have it, respectively. In Asia, however, it is between 0.4% and 0.7%. Every year, the number of new psoriasis cases increases.[2] Its incidence in Egypt is between 0.19 and 3%.[3]

Although the precise aetiology is unknown, psoriasis development is influenced by several risk factors, including genetics, trauma, infection, medications, and psychological stress.[4]

Plaque, guttate, inverted, pustular, and erythrodermic psoriasis are the five primary forms of the skin condition. About 90% of cases have plaque psoriasis, commonly referred to as psoriasis vulgaris. The two characteristic hallmarks of psoriasis pathogenesis include abnormal activation and proliferation of keratinocytes in the epidermis[5], together with chronic inflammation and lymphocytic infiltration in the underlying dermis.[5,6] Previous studies showed that cytokines secreted by dermal T lymphocytes' inflammatory infiltrate induce keratinocyte proliferation.[7]

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To encourage keratinocyte proliferation and the production of extracellular matrix, dermal fibroblasts are positioned beneath the basal epidermis layer. Exaggerated levels of certain cytokines, such as IL-6, CXCL8, and CXCL2, are released by these fibroblasts in psoriasis, which promotes the chemoattraction of T lymphocytes into the dermis along with epidermal hyperplasia, two characteristics of psoriasis. Cytokine production is regulated by Zinc Finger Protein 36 Homolog (ZFP36) family members.[8] Tristetraprolin (TTP), another name for ZFP36, is a ribonucleic acid (RNA) binding protein (RBP) that is important in controlling the production of mRNAs that contain adenylate-uridylate-rich regions (AREs). It can restrict the expression of several important genes that are commonly overexpressed in cancer and inflammation.[9] Additionally, it was shown that chronic inflammatory diseases that resemble psoriatic skin have decreased ZFP36 family protein expression.[8]

A 26-kD protein called interleukin (IL)6 has been shown to increase the production of antibodies by B lymphocytes.[10] Additionally, IL6 inhibits the differentiation of regulatory T cells (Treg) and encourages the specific differentiation of naive CD4+ T cells, which causes it to have a role in the emergence of certain chronic inflammatory and autoimmune illnesses, including psoriasis.[11] Therefore, anti-IL6 agents may potentially represent future promising target therapies for the treatment of psoriasis.[12]

Finally, dermal fibroblasts may have a prominent role in the regulation of inflammatory response in psoriasis. Their heightened inflammatory appearance is dependent on changes in ZFP36 family levels, which induce them to release exaggerated amounts of inflammatory cytokines such as IL6. However, the participation of dermal fibroblasts in psoriasis pathogenesis isn't well recognized. This study will look at ZFP 36 and IL6 immunohistochemical (IHC) expression in plaque psoriasis compared with healthy controls and correlate their expression with the available clinicopathological data to learn more about the disease's pathophysiology and to see if there are any treatment possibilities in the future.

## 2. Patients and methods

Computation of sample size.

The sample size was established based on the objectives and design of the research.

Study population.

Two groups participated in this case-control study: 30 patients with plaque psoriasis made up the case group, while 30 healthy people of the same age and sex made up the control group. Menoufia University Hospitals' Outpatient Clinics of Dermatology, Andrology, and STDs were the source of the patients. Participants in the Menoufia University Hospitals' Plastic Surgery Department served as control subjects between January and October 2022.

Inclusion criteria included patients with psoriasis vulgaris, irrespective of age and sex. All the studied cases were either newly diagnosed or had not received any systemic medication for 6 weeks or topical treatment except emollients for 15 days before sample collection. Patients with dermatologic diseases other than psoriasis vulgaris, other inflammatory, systemic diseases, or malignancy were excluded from the study. Diagnosis of cases based on patient history and typical clinical features confirmed by histopathological examination.[13]

A thorough history was taken from each participant, after which a general clinical and detailed dermatological examination was performed. The clinical evaluation of various psoriasis types was conducted using the Psoriasis Area and Severity Index (PASI) score.[14] Under 10, psoriasis is classified as mild, between 10 and 20, as moderate, and beyond 20, as severe, according to the PASI.[15]

Ethical Considerations.

The Ethics Committee on Human Rights at Menoufia University authorized the study before it began, and each participant provided written informed permission (IRB approval number and date: 6/2022 DERMA13).

Research plan.

Each patient or control case included a comprehensive history that included the patient's age and gender, onset, course, disease duration/years if their family background was favourable, sites affected, presence or absence of itching and kobernization, PASI score, and severity. In a clinical environment, psoriasis was diagnosed using a case definition. The clinical diagnosis was then confirmed by microscopic examinations and skin scrapings, and skin samples were taken for histological and immunohistochemical examinations.

Research population workup.

Skin biopsy.

The skin was well cleansed with spirit before the biopsy, and a little injection of a local anaesthetic (2% lignocaine) was administered. In addition to a biopsy from the site matched to the control individual, a punch biopsy of 3 mm in diameter was collected from the lesional and perilesional skin, and 1 cm from the psoriatic lesion, using a baker's punch.[16] Using a 10% formalin solution, the specimens were stored for histological examination.

Pathological analysis.

Before being embedded in paraffin blocks, each biopsy specimen was preserved in a 10% formalin solution, dehydrated in xylene, and graded in ethanol solution (100% concentration for 2 minutes, second concentration for 2 minutes, and third concentration for 2 minutes at 95% concentration). Formalin-fixed, paraffin-embedded slices (4 µm thick) were stained with hematoxylin and eosin for routine histological examination. To make the diagnosis, stained slides were inspected under a microscope.

Furthermore, slides were examined for epidermal acanthosis, hyperkeratosis, parakeratosis, Munro-microabcesses, suprapapillary epidermal thinning, spongiosis, and dermal inflammation.

ZFP36 and IL6 Immunohistochemical analysis.

The paraffin-embedded blocks were cut into many portions, which were then deparaffinized and rehydrated in 99% and 95% alcohol and xylene, respectively. After 20 minutes of boiling in 10 millilitres of citrate buffer (pH 6.0), the antigen was recovered and allowed to cool to room temperature. The slides were incubated for a whole night at room temperature with purified mouse monoclonal anti-ZFP36 (Catalog No. YPA2546, Chongqing Biospes Co., Ltd, China) and mouse monoclonal anti-IL6 (Catalog No. ab9324; Abcam, Cambridge, UK). Both were diluted to 1:30 for ZFP36 and 1:100 for IL6 using Phosphate Buffered Solution (PBS). After being deparaffinized with xylene, all slides were rehydrated with ethanol at gradually lower concentrations. Hydrogen peroxidase was added for 15 minutes to limit endogenous peroxidase activity. After applying the main antibody to the slides, they were placed in a humidity chamber and allowed to sit at room temperature for the whole night. Before undergoing another PBS wash, the sections underwent a secondary antibody treatment for 15 minutes after being rinsed with PBS.

Finally, for 20 minutes before a PBS wash, the bound antibody was detected using a modified labelled avidin-biotin reagent. A 0.1% diaminobenzidine solution was employed as a chromogen for five minutes. The slides were counterstained with Mayer's hematoxylin for five to ten minutes. ZFP36 and IL6 were tested using human brain and liver tumour tissue as positive controls, respectively. The primary antibody was used as a negative control.[17]

Analysis of ZFP36 and IL6 IHC findings:

A positive result was defined as any brown nuclear and/or cytoplasmic staining in dermal fibroblasts, inflammatory cells, or epidermal keratinocytes in the cases and control tissues under examination.

Both ZFP36 and IL6 were evaluated as positive or negative in epidermal keratinocytes. Additionally, the following marker expressions were evaluated: expression percentage[18], stain's intensity is categorized as light (+), moderate (++), or high (+++), Histo-score (H score) using the following formula: 1 X% of cells were lightly stained, 2 X% were moderately stained, and 3 X% were strongly stained. A value ranging from 0 to 300 was then assigned. [19]

In relation to inflammatory cells and dermal fibroblasts, ZFP36 and IL6 were evaluated as positive or negative. Moreover, the mean ± Standard Deviation (SD) was used to indicate the number of positive cells per 10 HPFs.

Analytical statistics.

Following a normality test, the various variables were shown as medians, mean ± standard deviation (SD), percentages (%), and numbers (No.). When comparing quantitative variables between two sets of regularly distributed data, the Student's t-test was employed, and when comparing non-normally distributed data, the Mann-Whitney test was employed. Spearman correlation (r) was used to show how two continuous, non-normally distributed variables were correlated. Associations between qualitative factors were examined using the chi-square test (x2). If there were fewer than five expected cells, Fisher's Exact test was used. The Mc Nemar test and marginal homogeneity were employed to examine the relationships between related qualitative variables. If the two-sided P-value was less than 0.05, it was considered statistically significant.

## 3. Results

Initial attributes of the individuals involved.

Regarding age and sex, there was no discernible difference between cases and controls. Table 1 displays the clinical information of the psoriasis cases under study.

*Table 1. Demographic and clinical data for the studied groups.*

| STUDIED VARIABLES | PATIENTS (NO=30) | | CONTROLS (NO=30) | | P VALUE |
|---|---|---|---|---|---|
| | No. | % | No. | % | |
| AGE / YEARS | | | | | 0.668 |
| MEAN ±SD | 45.4±15.2 | | 45.3±14.2 | | |
| MEDIAN | 50.0 | | 46.5 | | |
| RANGE | 15.0 – 65.0 | | 15.0 - 70.0 | | |
| SEX | | | | | 1.00 |
| MALE | 22 | 73.3 | 22 | 73.3 | |
| FEMALE | 8 | 26.7 | 8 | 26.7 | |
| ONSET | | | ---- | | ---- |
| EARLY | 10 | 33.3 | | | |
| LATE | 20 | 66.7 | | | |
| COURSE | | | ---- | | ---- |
| STATIONARY | 11 | 36.7 | | | |
| PROGRESSIVE | 19 | 63.3 | | | |
| DISEASE DURATION / YEARS | | | ---- | | ---- |
| MEAN ±SD | 5.46±3.35 | | | | |
| MEDIAN | 5.00 | | | | |
| RANGE | 1.00 – 10.0 | | | | |
| FAMILY HISTORY | | | ---- | | ---- |
| POSITIVE | 10 | 33.3 | | | |
| NEGATIVE | 20 | 66.7 | | | |

| | | | | |
|---|---|---|---|---|
| RISK FACTORS | | | ---- | ---- |
| NO | 18 | 60.0 | | |
| DM | 4 | 13.3 | | |
| HTN | 5 | 16.7 | | |
| SMOKING | 3 | 10.0 | | |
| SITE AFFECTED | | | ---- | ---- |
| AXIAL | 5 | 16.7 | | |
| EXTREMITIES | 15 | 50.0 | | |
| AXIAL &EXTREMITIES | 10 | 33.3 | | |
| SCALP AFFECTION | | | ---- | ---- |
| YES | 16 | 53.3 | | |
| NO | 14 | 46.7 | | |
| NAIL AFFECTION | | | ---- | ---- |
| YES | 8 | 26.7 | | |
| NO | 22 | 73.3 | | |
| JOINT AFFECTION | | | ---- | ---- |
| YES | 10 | 33.3 | | |
| NO | 20 | 66.7 | | |
| PALM AND SOLE AFFECTION | | | ---- | ---- |
| YES | 11 | 36.7 | | |
| NO | 19 | 63.3 | | |
| ITCHING | | | ---- | ---- |
| YES | 24 | 80.0 | | |
| NO | 6 | 20.0 | | |
| KOBERNIZATION | | | ---- | ---- |
| YES | 8 | 26.7 | | |
| NO | 22 | 73.3 | | |
| PASI | | | ---- | ---- |
| MEAN ±SD | 15.8 ±13.3 | | | |
| MEDIAN | 10.7 | | | |
| RANGE | 3.00 – 68.0 | | | |
| SEVERITY | | | ---- | ---- |
| MILD | 10 | 33.3 | | |
| MODERATE | 10 | 33.3 | | |
| SEVERE | 10 | 33.3 | | |

No: number %: percentage SD: standard deviation DM: Diabetes mellitus HTN: Hypertension PASI: Psoriasis area and severity index

Histopathological examination.

Epidermis and underlying dermis of all control subjects revealed no remarkable pathological abnormality (Figure 1). Histopathological examination in lesional skin of psoriasis cases revealed marked acanthosis in 40%, marked hyperkeratosis in 33.3%, marked parakeratosis in 20%, munro-micro abscesses in 53.3%, supra-papillary epidermal thinning in 70% and spongiosis in 83.3% of cases together with absent granular layer in all cases. Also, dermal inflammation was marked at 53.3% (Fig. 1). A significant difference was found in the degree of severity of histopathological criteria between lesional and prelesional skin of psoriasis cases (Figure 1) & (Table 2).

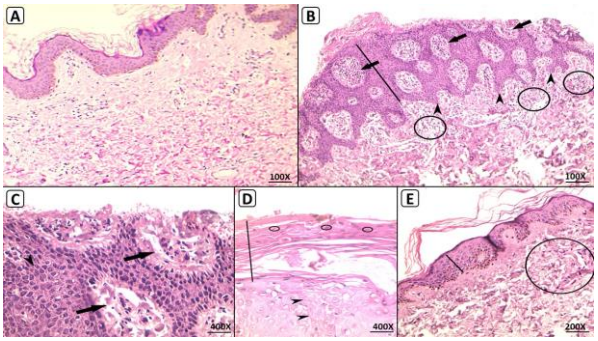


Figure 1. Histopathological changes in studied groups. (A) The control group showed normal epidermal covering and underlying dermis with no remarkable pathological abnormality. (B) Lesional skin from the psoriasis patient showed marked acanthosis (black line), Munro-microabscesses (black arrows), supra-papillary epidermal thinning (arrowheads) and marked infiltration by dermal inflammatory cells (circles). (C) Higher magnification of the same psoriasis case demonstrating Munro-microabscesses (black arrows) and mild spongiosis (arrowheads). (D) Lesional skin from another psoriasis patient showed marked hyperkeratosis (black line) and parakeratosis (black circles). (E ) Prelesional skin from psoriasis patient with mild acanthosis (black line) and mild dermal inflammatory infiltrate (circle). (Magnification: 100× for A & B, 400× for C&D and 200x for E).

*Table 2. Histopathological findings of the studied psoriasis cases (No=30).*

| STUDIED VARIABLES | LESIONAL | | PERILESIONAL | | TEST OF SIG. | P VALUE |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | | |
| ACANTHOSIS | | | | | MH | |
| MILD | 10 | 33.3 | 1 | 3.30 | 52.8 | <0.001* |
| MODERATE | 8 | 26.7 | 1 | 3.30 | | |
| MARKED | 12 | 40.0 | 0 | 0.00 | | |
| NO | 0 | 0.00 | 28 | 93.4 | | |
| HYPER KERATOSIS | 10 | 33.3 | 22 | 73.3 | MH 14.7 | <0.001* |
| MILD | 10 | 33.3 | 8 | 26.7 | | |
| MODERATE | 10 | 33.3 | 0 | 0.00 | | |
| MARKED | | | | | | |
| PARA KERATOSIS | | | | | MH | |
| MILD | 12 | 40.0 | 10 | 33.3. | 20.9 | <0.001* |
| MODERATE | 10 | 33.3 | 2 | 6.70 | | |
| MARKED | 6 | 20.0 | 1 | 3.3. | | |
| NO | 2 | 6.70 | 17 | 56.7 | | |
| MUNRO-MICROABSCESS | 16 | 53.3 | 3 | 10.0 | Mc 13.0 | <0.001* |
| PRESENT | 14 | 46.7 | 27 | 90.0 | | |
| ABSENT | | | | | | |
| SUPRAPAPILLARY EPIDERMIS THINNING | 21 | 70.0 | 4 | 13.3 | Mc 19.8 | <0.001* |
| PRESENT | 9 | 30.0 | 26 | 86.7 | | |
| ABSENT | | | | | | |
| SPONGIOSIS | | | | | Mc | |
| PRESENT | 25 | 83.3 | 9 | 30.0 | 17.4 | <0.001* |
| ABSENT | 5 | 16.7 | 21 | 70.0 | | |
| GRANULAR LAYER | 0 | 0 | 30 | 100 | Mc 35.6 | <0.001* |
| PRESENT | 30 | 100 | 0 | 0 | | |
| ABSENT | | | | | | |
| DERMAL INFLAMMATION | 3 | 10.0 | 23 | 76.7 | MH 35.6 | <0.001* |
| MILD | 11 | 36.7 | 5 | 16.7 | | |
| MODERATE | 16 | 53.3 | 0 | 0.00 | | |
| MARKED | 0 | 0.00 | 2 | 6.60 | | |
| NO | | | | | | |

No: number %: percentage MH:Marginal homogeneity test Mc: Mc Nemar test * significant

ZFP36 and IL6 Immunohistochemical Outcomes.

ZFP36's epidermal and dermal IHC expression in the groups under study:

In the control group, ZFP36 was positive in the epidermis in all cases with an average of the total percentage of positive cells of 84.6±13.1, H-score 165.6±68.1 and in dermis 70% with a mean value of positive cell count/10HPF of 7.28±5.58. However, in the lesional skin of psoriatic patients, ZFP36 was positive in the epidermis in 80% with epidermal total per cent of positive cells mean value of 31.4±19.1 and H-

score of 55.4±41.2, while in the dermis in 73.3% with mean value of the dermal positive cell count/10HPF of 35.8±29.2. Regarding perilesional skin of psoriatic patients, ZFP36 was positive in the epidermis in 83.3% with epidermal total per cent of positive cells mean value of 63.1±20.8 and H-score of 147.2±83.1, while in the dermis in 56.7% with dermal positive cell count/10HPF mean value of 31.5±51.7. A statistically significant difference regarding epidermal ZFP36 positivity, total percent of positive cells and H-score mean values was detected between lesional, prelesional skin and controls (P=0.04, 0.001 and 0.001; respectively) with the highest values detected in control skin and decreased in prelesional skin and the lowest values were in lesional skin. Also, a significant difference was found between the number of positive dermal cells in lesional, prelesional skin and controls (P=0.001) with the highest values detected in lesional skin and decreased in prelesional skin and the lowest values in controls (Figure 2&3).

IL6's epidermal and dermal IHC expression in the groups under study:

Regarding the control group, IL6 was positive in the epidermis in all cases with a total per cent of positive cells mean value of 65.3±30.8, H-score 88.3±54.7 and negative in the dermis in all cases. However, in the lesional skin of psoriatic patients, IL6 was positive in the epidermis in 40% with epidermal total per cent of positive cells mean value of 28.7±27.3 and H-score of 37.9±27.8, while in the dermis in 43.3% with dermal positive cell count/10HPF mean value of 12.1±10.4. Regarding perilesional skin of psoriatic patients, IL6 was positive in the epidermis in 50% with epidermal total per cent of positive cells mean value of 58.0±27.5 and H-score of 101.3±59.6, while in the dermis in 40% with mean value of dermal positive cell count/10HPF of 11.3±6.56. A statistically significant difference regarding epidermal IL6 positivity, total percent of positive cells and H-score mean values was detected between lesional, prelesional skin and controls (P= 0.001) with the highest values detected in control skin and decreased in prelesional skin and the lowest values were in lesional skin. Also, a significant difference was found regarding dermal IL6 positivity in lesional, and prelesional skin and controls (P=0.001) with the highest values detected in lesional skin and decreased in prelesional skin and the lowest values in controls (Figure 2&3).

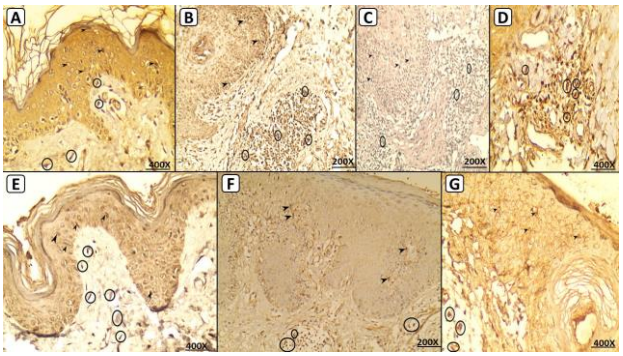


Figure 2. ZFP36 and IL6 IHC in studied groups. Skin biopsy from the control group showed many ZFP36 (A) and IL6 (E) positive epidermal cells with strong intensity (arrowheads) and completely negative dermal cells (circles). Lesional skin showing ZFP36 (B) and IL6 (F) positive epidermal cells with moderate intensity (arrowheads) and many positive dermal cells (circles). (C) Prelesional skin with completely ZFP36 negative epidermal (arrowheads) and dermal cells (circles). (D) Another perilesional skin with ZFP36 positive dermal cells (circles) are fewer than lesional skin. (G) Prelesional skin with IL6-positive epidermal (arrowheads) and dermal cells (circles). (Magnification: 400× for A, D, E, G and 200× for B, C&F).

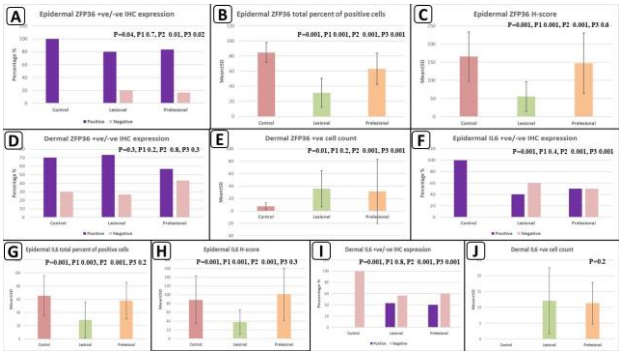


Figure 3. Epidermal and dermal expression of ZFP36 and IL6 between control, lesional and prelesional skin. Epidermal ZFP36 (A) and IL6 (F) +ve /-ve IHC expression. Epidermal ZFP36 (B) and IL6 (G) total per cent of positive cells. Epidermal ZFP36 (C) and IL6 (H) H- score. Dermal ZFP36 (D) and IL6 (I) +ve /-ve IHC expression. Dermal ZFP36 (E) and IL6 (J) +ve cell count. Data are expressed as percentage in (A) & (D) and mean ± SD in (B), (C) & (E) with statistically significant difference in (A), (B), (C), (E), (F), (G), (H) & (I) (P=0.04, 0.001, 0.001, 0.01, 0.001, 0.001, 0.001 & 0.001 respectively) and no significant difference (P=0.3, 0.2) in (D) & (J); respectively, P1: Comparison between lesional and perilesional, P2: Comparison between lesional and control and P3: Comparison between perilesional and control.

ZFP36 and IL6 expression in the skin lesions of psoriasis patients: a correlation between the

epidermal and dermal expression.

Dermal ZFP36 expression and epidermal IL6 showed a significantly significant negative connection (r= -0.069 and P= 0.03) (Figure 4) and (Table 3).

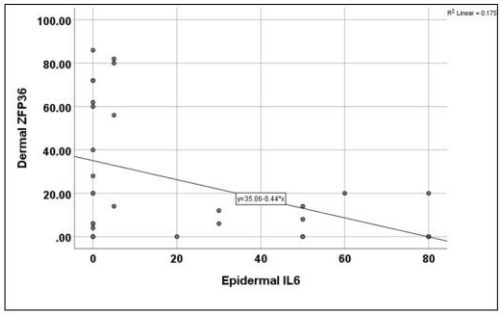


Figure 4. A significant negative correlation between epidermal IL6 and dermal ZFP36 IHC expression in lesional skin of psoriasis patients.

*Table 3. Correlation between ZFP36 IL6 expression in lesional skin of psorisasis patients.*

| STUDIED VARIABLES | EPIDERMAL ZFP36 | | DERMAL ZFP36 | | EPIDERMAL IL6 | | DERMAL IL6 | |
|---|---|---|---|---|---|---|---|---|
| | r | P value | r | P value | r | P value | r | P value |
| EPIDERMAL ZFP36 | - | - | -0.19 | 0.401 | 0.35 | 0.32 | 0.09 | 0.78 |
| DERMAL ZFP36 | -0.19 | 0.4 | - | - | -0.69 | 0.03* | -0.46 | 0.14 |
| EPIDERMAL IL6 | 0.35 | 0.32 | -0.69 | 0.03* | - | - | 0.63 | 0.13 |
| DERMAL IL6 | 0.09 | 0.78 | -0.45 | 0.14 | 0.63 | 0.13 | - | - |

r: Spearman's correlation *Significant

The relationship between epidermal (total % of positive cells) and dermal (number of +ve cells/10HPFs) ZFP36 expression in psoriasis patients' lesional skin with clinical and histopathological parameters.

Regarding epidermal ZFP36 expression, the total percentage of positive cells of lesional skin was much greater in women than in men (P=0.004). No other significant relationship was found between epidermal or dermal ZFP36 expression and clinical or histopathological findings of psoriasis cases (Table 4).

*Table 4. Association between epidermal (total % of positive cells) and dermal (number of +ve cells/ 10HPFs) ZFP36 expression in lesional skin with clinical and histopathological parameters.*

| STUDIED VARIABLES | EPIDERMAL ZFP36 Mean±SD | P VALUE | DERMAL ZFP36 Mean±SD | P VALUE |
|---|---|---|---|---|
| SEX | | | | |
| MALE | 17.9±16.1 | 0.004** | 39.7±29.9 | 0.29 |
| FEMALE | 45.0±22.0 | | 27.4±27.9 | |
| ONSET | | | | |
| EARLY | 36.5±25.1 | 0.09 | 30.0±32.1 | 0.39 |
| LATE | 19.5±17.0 | | 38.5±28.5 | |
| COURSE | | | | |
| STATIONARY | 35.0±23.3 | 0.06 | 25.0±25.3 | 0.22 |
| PROGRESSIVE | 19.4±18.3 | | 42.0±30.3 | |
| FAMILY HISTORY | | | | |
| POSITIVE | 23.0±24.5 | 0.53 | 34.2±28.7 | 0.92 |
| NEGATIVE | 26.2±20.1 | | 36.7±30.5 | |
| RISK FACTORS | | | | |
| NO | 50.8±44.1 | 0.51 | 32.3±29.1 | 0.72 |
| DM | 57.5±65.5 | | 44.5±32.8 | |
| HTN | 28.0±22.8 | | 34.0±45.2 | |
| SMOKING | 15.0±15.0 | | 40.0±20.0 | |
| ACANTHOSIS | | | | |
| MILD | 36.5±22.8 | 0.06 | 32.2±29.4 | 0.83 |
| MODERATE | 11.8±14.6 | | 36.8±30.9 | |
| MARKED | 24.5±19.7 | | 37.8±31.2 | |
| HYPER KERATOSIS | 36.5±22.8 | 0.16 | 32.2±29.4 | 0.76 |
| MILD | 18.0±14.9 | | 42.2±32.9 | |
| MODERATE | 21.0±22.3 | | 32.0±27.7 | |
| MARKED | | | | |
| PARA KERATOSIS | | | | |
| MILD | 12.9±12.5 | 0.05 | 50.3±34.2 | 0.63 |
| MODERATE | 28.5±21.6 | | 26.0±24.1 | |
| MARKED | 34.1±19.0 | | 40.6±31.2 | |
| NO | 55.0±35.3 | | 17.0±15.5 | |
| MUNRO MICROABSCESS | 25.9±22.8 | 0.88 | 40.9±29.5 | 0.23 |
| PRESENT | 24.2±20.1 | | 28.4±28.7 | |
| ABSENT | | | | |
| SUPRAPAPILLARY EPIDERMIS THINNING | 27.6±18.7 | 0.14 | 37.5±28.8 | 0.53 |
| PRESENT | 19.4±26.7 | | 31.3±32.5 | |
| ABSENT | | | | |
| SPONGIOSIS | | | | |
| PRESENT | 26.4±22.1 | 0.76 | 39.4±29.7 | 0.14 |
| ABSENT | 19.0±17.4 | | 12.6±8.08 | |
| DERMAL INFLAMMATION | 33.3±41.6 | 0.76 | 46.0±56.5 | 0.1 |
| MILD | 24.5±17.5 | | 18.2±18.4 | |
| MODERATE | 24.0±20.6 | | 43.6±28.2 | |
| MARKED | | | | |

The relationship between epidermal (total % of positive cells) and dermal (number of +ve cells/10HPFs) IL6 expression in psoriasis patients' lesional skin with clinical and histopathological parameters.

Regarding epidermal IL6 expression, the mean total per cent of positive cells was significantly higher in cases with stationary course of disease (P=0.02) and in cases with marked parakeratosis (P=0.04). Regarding dermal expression, no significant relationship was found with either clinical or histopathological findings of the studied cases (Table 5).

*Table 5. The relationship between epidermal (total % of positive cells) and dermal (number of +ve cells/ 10HPFs) IL6 expression in lesional skin of psoriasis patients with clinical and histopathological parameters.*

| STUDIED VARIABLES | EPIDERMAL IL6 Mean±SD | P VALUE | DERMAL IL6 Mean±SD | P VALUE |
|---|---|---|---|---|
| SEX | | | | |
| MALE | 30.5±29.7 | 0.93 | 10.2±9.67 | 0.121 |
| FEMALE | 23.3±23.1 | | 18.7±12.2 | |
| ONSET | | | | |
| EARLY | 33.3±15.2 | 0.30 | 11.1±9.97 | 0.467 |
| LATE | 27.2±31.0 | | 13.3±11.7 | |
| COURSE | | | | |
| STATIONARY | 57.5±28.7 | 0.02* | 14.4±12.7 | 0.456 |
| PROGRESSIVE | 14.3±10.8 | | 10.7±9.36 | |
| FAMILY HISTORY | | | | |
| POSITIVE | 34.1±26.9 | 0.33 | 8.00±4.14 | 0.309 |
| NEGATIVE | 23.3±29.2 | | 15.7±13.0 | |
| RISK FACTORS | | | | |
| NO | 32.5±28.2 | 0.26 | 13.5±12.1 | 0.230 |
| DM | 7.50±3.53 | | 10.6±4.61 | |
| HTN | 18.3±12.5 | | 4.00±0.00 | |
| SMOKING | 8.00±0.00 | | - | |
| ACANTHOSIS | | | | |
| MILD | 50.0±30.0 | 0.16 | 15.5±11.8 | 0.148 |
| MODERATE | 38.3±38.1 | | 22.0±19.7 | |
| MARKED | 13.3±9.83 | | 7.42±4.07 | |

| | | | | |
|---|---|---|---|---|
| HYPER KERATOSIS | 50.0±30.0 | 0.28 | 15.5±11.8 | 0.397 |
| MILD | 26.0±31.8 | | 12.8±13.0 | |
| MODERATE | 16.2±11.0 | | 8.00±5.35 | |
| MARKED | | | | |
| PARA KERATOSIS | | | | |
| MILD | 5.00±0.00 | 0.04* | 15.0±12.3 | 0.756 |
| MODERATE | 20.0±10.0 | | 13.2±15.1 | |
| MARKED | 44.0±33.6 | | 7.00±1.73 | |
| | | | 12.0±5.65 | |
| MUNRO MICROABSCESS | 25.0±28.6 | 0.52 | 12.1±11.1 | 0.884 |
| PRESENT | 32.5±28.2 | | 12.1±10.5 | |
| ABSENT | | | | |
| SUPRAPAPILLARY EPIDERMIS THINNING | 31.2±31.2 | 0.86 | 13.1±12.4 | 0.432 |
| PRESENT | 23.7±20.5 | | 10.0±4.00 | |
| ABSENT | | | | |
| SPONGIOSIS | | | | |
| PRESENT | 25.5±23.9 | 0.51 | 10.1±7.91 | 0.102 |
| ABSENT | 45.0±49.4 | | 16.0±0.00 | |
| DERMAL INFLAMMATION | 27.5±31.8 | 0.68 | 10.0±8.48 | 0.741 |
| MILD | 30.0±0.00 | | 15.2±12.0 | |
| MODERATE | 28.7±32.1 | | 11.0±10.4 | |
| MARKED | | | | |

## 4. Discussion

Our study provides valuable insights into the IHC expression of ZFP36 and IL6 in plaque psoriasis compared with healthy controls, highlighting their potential roles in the disease pathology and exploring whether there are any treatment possibilities in the future.

Through ZFP36 direct targeting and destabilization of mRNAs encoding proinflammatory cytokines, it plays a critical role in downregulating inflammatory responses. [20,8] However, to our knowledge, no previous study had investigated the expression of ZFP36 at the protein level using immunostaining in psoriasis to determine its role in disease pathogenesis. Most studies have focused on genetic analysis rather than immunostaining.[8,20,21] It is well known that immunostaining is a simple technique that is much easier than performing PCR or genetic analysis. It is a single-step technique, highly applicable, and cost-effective. Therefore, it can be used more frequently in routine practice and may be a more convenient option.[22] Moreover, we studied ZFP36 IHC expression in epidermal keratinocytes and dermal cells, including fibroblasts and inflammatory cells, and not only in fibroblasts, as ZFP36 protein was found to be expressed not only in dermal fibroblasts but also in keratinocytes, macrophages, and dendritic cells.[23] Our findings indicate a significant reduction in epidermal ZFP36 expression in lesional psoriatic skin compared to prelesional and control skin, with the lowest values in the fully developed lesions (P=0.04, 0.001, and 0.001, respectively). This aligns with previous studies[23,21] suggesting that down-regulation of ZFP36 contributes to sustained inflammation in psoriasis by failing to degrade proinflammatory cytokine mRNAs such as IL6, TNF-α, and IL17A.[20,8] Furthermore, decreased ZFP36 expression in perilesional skin relative to control skin may signify an initial molecular event that predisposes the skin to inflammatory lesions following subsequent triggers such as Köbnerization.[24]

Interestingly, dermal ZFP36 expression showed an inverse pattern, with the highest number of positive cells (including dermal fibroblasts and inflammatory cells) detected in lesional skin and decreasing values in prelesional and control skin (P=0.001). However, previous studies documented that ZFP36 family members, whose expression is decreased in psoriasis dermal fibroblasts contributing to the inflammatory cascade, govern the production of inflammatory mediators by dermal fibroblasts from lesional psoriatic skin.[8] Additionally, ZFP36 is downregulated in dermal fibroblasts isolated from psoriasis sufferers' skin as opposed to those isolated from healthy people, according to Haneklaus et al.[25]

This paradoxical increase in the dermis may reflect a compensatory upregulation in response to chronic inflammation, as previously observed in inflammatory skin diseases. However, this upregulation appears insufficient to counteract the inflammatory cascade in psoriatic lesions. Another possible explanation for this discrepancy is that we observed ZFP36 not only in dermal fibroblasts but also in inflammatory cells.

IL-6 is a proinflammatory cytokine that is generated by various cell types and has different physiologic effects on multiple cell types.[26] Also, it is a key cytokine in psoriatic pathogenesis, promoting keratinocyte proliferation and immune cell activation.[27] Our results demonstrate a significant decrease in epidermal IL6 expression in lesional skin compared to prelesional and control groups (P=0.001), whereas dermal IL6 expression was highest in lesional skin and progressively lower in prelesional and control groups (P=0.001). The dermal expression pattern of IL6 in our study was similar to that observed by Castells-Rodellas A et al., where IL-6 positivity in the dermis was higher in lesional samples compared to non-lesional and control samples.[28] This suggests that in established lesions, IL6 activity is more pronounced in the dermis, possibly driven by infiltrating immune cells rather than keratinocytes.[28] Blauvelt A. also posited that an absence of epidermal IL6 resulted in compensatory proinflammatory responses from other cytokines, ultimately exacerbating psoriatic inflammation.[27]

The observed negative correlation between epidermal IL6 and dermal ZFP36 expression (r = -0.069, P=0.03) further supports the notion that ZFP36 downregulation in keratinocytes may lead to increased IL6 expression and prolonged

inflammation.[8] Our findings suggest that restoring ZFP36 levels could serve as a potential therapeutic approach to counteract IL6-mediated inflammation.

Epidermal ZFP36 expression in lesional skin in our thesis was significantly higher in female patients compared to males (P=0.004), suggesting potential sex-related differences in ZFP36-mediated inflammatory regulation. Those results were supported by a previous study, which suggested that variations in ZFP36 expression could be attributed to gender differences.[29] The study found that TTP down-regulation was linked to worse overall survival in male hepatocellular cancer patients but not in female patients. Furthermore, the production of the proinflammatory cytokine IL6, which has been shown to promote hepatocarcinogenesis in a gender-dependent way, was also shown to be inhibited by liver-specific ZFP36 deletion. Another study found that serum ZFP36 levels differed significantly between males and females.[30] The researchers found that serum ZFP36 levels had a significant positive relationship with insulin resistance in males with metabolic syndrome, but not in females. These differences could result from sex-specific variations in ZFP36 gene expression upon cellular stimuli or differences in adipose tissue composition. No other significant associations were observed between ZFP36 expression and clinical or histopathological parameters, agreeing with those who did not report any significant associations between ZFP36 expression and clinical or histopathological parameters.[31]

Conversely, epidermal IL6 expression was significantly elevated in cases with a stationary disease course (P=0.02) and those exhibiting marked parakeratosis (P=0.04). This suggests that IL6 may contribute to maintaining chronic inflammation and abnormal keratinocyte differentiation, both hallmarks of psoriasis. Saggini A. et al. documented that increased IL6 expression has been associated with the inflammatory activity in psoriasis and serves as an indicator of treatment response.[12] Regarding parakeratosis, IL6 is known to influence keratinocyte proliferation and differentiation. Parakeratosis, characterized by the retention of nuclei in the stratum corneum, reflects abnormal keratinocyte maturation. IL6, along with other cytokines, stimulates keratinocytes to proliferate, contributing to the psoriatic phenotype.[32] While direct studies linking IL6 expression specifically to parakeratosis are limited.

Our findings underscore the dual role of ZFP36 in epidermal suppression and dermal compensation of inflammation, further supporting its role as a negative regulator of cytokine signalling in psoriasis. The observed inverse relationship between ZFP36 and IL6 suggests a potential therapeutic target where modulating ZFP36 expression could mitigate psoriatic inflammation.

Future studies should focus on determining how ZFP36 modulation influences IL6 and other cytokines in psoriasis, assessing whether ZFP36 levels fluctuate with disease progression and treatment response, together with therapeutic trials exploring ZFP36 regulatory function in psoriatic skin.

### *4. Conclusion*

Our study demonstrates significant alterations in ZFP36 and IL6 expression in psoriatic skin, highlighting their potential interplay in disease pathogenesis. The inverse correlation between dermal ZFP36 and epidermal IL6 suggests a disrupted regulatory mechanism, contributing to persistent inflammation in psoriasis. These findings open avenues for exploring ZFP36-based therapeutic interventions, which could offer new strategies for managing psoriatic disease.

## Disclosure

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## Authorship

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