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Cytokine Dysregulation in Psoriasis: A Comparative Study of Pro-inflammatory TNF-α and Regulatory IL-35

Sara M. AL-Hussaini[1*], Haider H. Mohammed Ali[1], and Osama Niema Alhemiari[2]

[1]*Dept. of Biology, College of Science, University of Kerbala, Iraq.*

[2] *MOH, Kerbala Health Directorate, Imam Alhassan Teaching Hospital Consultant Dermatologist, Iraq.*

***Corresponding Author Email:** saraalhussaini728@gmail.com

ABSTRACT

Background: *A prevalent inflammatory skin condition is psoriasis; massive inflammatory cell infiltration and aberrant epidermal keratinocyte growth are hallmarks of it. The cytokines released by activated resident immune cells, an infiltration of T cells, dendritic cells, and innate immune system cells, as well as the keratinocytes themselves, are what cause this hyperproliferation. The goal aim of current study, is detect TNF-α and IL-35 roles and the effect of microbiome dysbiosis in psoriatic patients. A total 100 samples (blood and swabs) were collected from patients with psoriasis and control groups from Kerbala governorate, Iraq. All swabs were cultured on blood and MacConkey agar. TNF-α and IL-35 were detected by ELISA technique. The result exhibited only 14 (28%) of the culture showed positive bacterial growth, the isolates were identified as Staphylococcus spp. and Pantoea spp. ELISA revealed that an increase TNF-α and IL-35 levels in psoriatic patients compared to healthy without significant differences. The study concluded that a link between bacterial presence and immune activity in psoriatic patients.*

Keywords: Psoriasis, Cytokines, TNF-α, IL-35, Microbiome dysbiosis.

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INTRODUCTION

Psoriasis is an immune system-mediated chronic inflammatory skin condition. Massive inflammatory cell infiltration and aberrant epidermal keratinocytes with abnormal growth are the hallmarks of psoriasis, a common inflammatory skin condition. Numerous cell types, including keratinocytes, T lymphocytes, dendritic cells, neutrophils, and macrophages, are said to be crucial to the development and course of psoriasis. It has been discovered that T cells, with their several subtypes, are important in immune-mediated illnesses, like psoriasis (Zhang *et al*., 2023; Wu *et al*., 2024).

Immune homeostasis and self-tolerance are controlled under regulatory T cells (Tregs), a subpopulation of $CD4^+$ T cells with immunosuppressive characteristics. Tregs, which are distinguished by their immunosuppressive properties and dependence on the transcription factor Foxp3 (Forkhead box protein P3), use a variety of pathways, such as cell contact inhibition, metabolic regulation, and cytokine secretion, to limit excessive immune activation and prevent autoimmunity while preserving tissue repair processes (Wang *et al*., 2025).

The potent proinflammatory cytokine is TNF-α, which is physiologically produced by a variety of cell types, including immune cells such as T lymphocytes, macrophages, and

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natural killer cells. It is primarily involved in physiological or disease processes, such as the reaction to invasive microorganisms and the inflammation that follows in the invaded area. It has long been believed that one of the primary causes of TNF-α generation is bacterial lipopolysaccharide (Zou *et al*., 2015; Li *et al*., 2023).Due to its immunomodulatory characteristics, tumor necrosis factor-alpha is believed to contribute to the pathophysiology of psoriasis. TNF-α accelerates keratinocyte proliferation in psoriasis by stimulating innate immune cell activation and trafficking to the skin (Ayala-Fontánez *et al*., 2021). Both immunoregulatory cell populations and immunosuppressive cytokines maintain the equilibrium between inflammatory and anti-inflammatory immune responses. In order to reduce inflammatory reactions in a normal state, interleukin-35 (IL-35), an inhibitory cytokine that is a member of the IL-12 family, can effectively decrease T cell proliferation and generate IL-35-producing induced regulatory T cells (iTr35) (Ye *et al*., 2021).

External stimuli, including stress, chemicals, or pathogens, might cause the initial phase of psoriasis by causing host cells to produce nucleotides in addition to some opportunistic microorganisms (Olejniczak-Staruch *et al*., 2021). So, in vulnerable people, alterations in the skin microbiome's makeup can set off inflammatory processes that result in inflammatory skin disorders (Celoria *et al*., 2023). By encouraging pro-inflammatory reactions, compromising skin barrier functioning, or causing autoimmunity through molecular mimicry, this microbial imbalance or dysbiosis may trigger distinctive inflammatory responses to psoriasis (Lewis *et al*., 2019).

Skin cells in psoriasis begin to proliferate up to ten times more quickly than in the usual state. It is an immune-mediated illness that makes the body inflamed. This occurs as a result of the system's overactivity, which speeds up the proliferation of somatic cells. Over the course of a month, normal skin cells fully develop and disappear (Kumari *et al*., 2021).

MATERIAL AND METHODS

Design of the Study: The current study was designed as a case-control type.

The collected of Samples: A total of 50 samples were collected from psoriatic patients and 50 healthy controls (without any autoimmune disease or other disease), included blood and swabs, those patients attending at Imam Hassan Al-Mujtaba Teaching Hospital in Kerbala during the period December 2024 to May 2025.

A sterile cotton swabs were inoculated on blood and MacConkey agar media, then stored at 37ºC in an aerobic environment for 24 hrs. The ELISA method was dependent on measuring TNF-α and IL-35 levels. Psoriasis patients and healthy volunteers had two milliliters of whole blood collected with a syringe, which was then put in a gel tube to separate serum for ELISA. A human IL-35 antibody has been pre-coated on the plate. The sample's IL-35 is introduced, and it attaches itself to the wells' coated antibodies. Then, a biotinylated human IL-35 antibody was added, and it attaches itself to the sample's IL-35. The biotinylated IL-35 antibody is bound by streptavidin-horseradish peroxidase (HRP). The next step was incubation; unbound streptavidin-HRP was washed away. The substrate solution responsible for color changes was added. The reaction was stopped by the addition of an acidic stop solution, and optical density was measured at 450 nm.

RESULTS AND DISCUSSION

The Immunological study

Serum levels of TNF- α were higher in the psoriatic patients with bacterial infections group (233.66) ng/ml compared with the patients without bacterial infection group (195.26) ng/ml and the control group (166.33) ng/ml (Figure 1). In addition, showed that no

significant difference for psoriatic patient's groups compared to the control group. Psoriasis may develop and progress as a result of TNF-α dysfunction (Pocino *et al*., 2024).

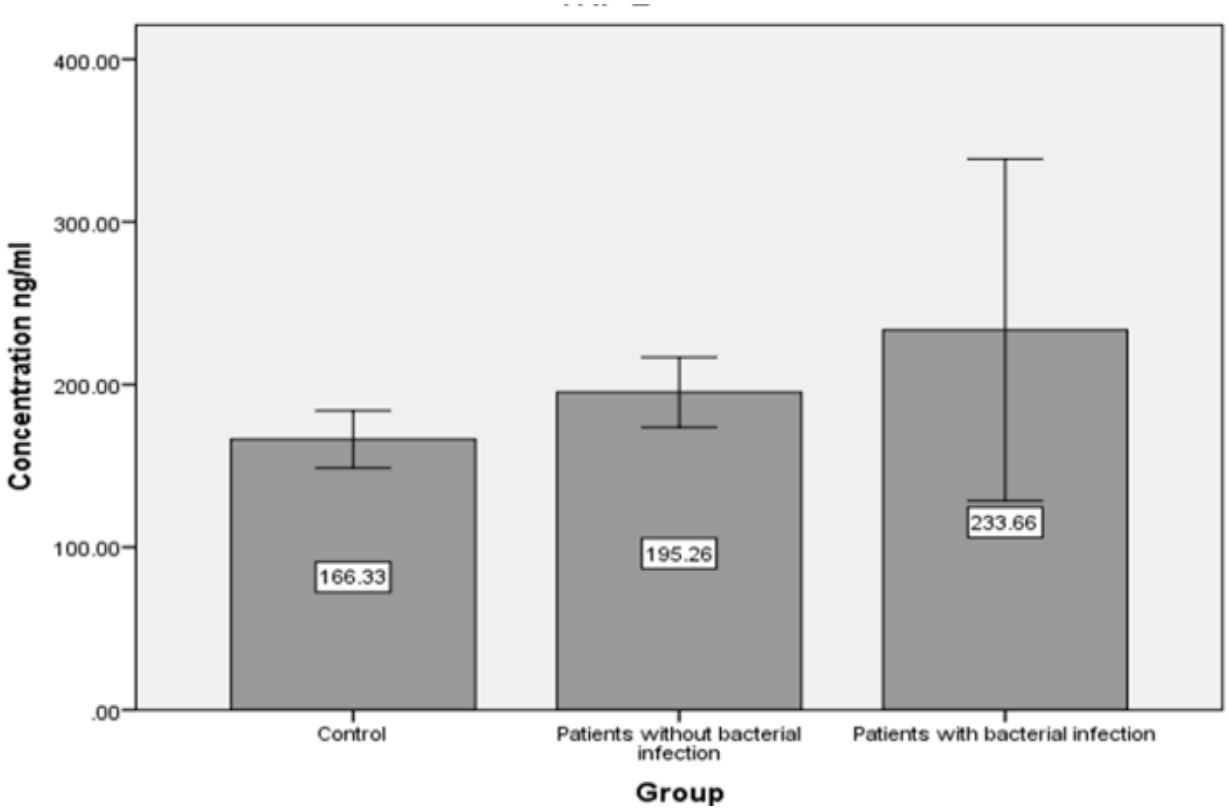

Figure 1: The con. of TNF- α in study population.

Hagag et al. (2021) found that the patient group's serum TNF-α levels are higher than those of the control group. In contrast to Wang et al. (2022), who claimed that TNF-α, a proinflammatory cytokine, plays an important role in the pathogenesis of psoriasis because it stimulates the nuclear factor (NF)-κB signal pathway, which influences cell survival, proliferation, and anti-apoptotic impact of lymphocytes and keratinocytes (Wang and Zhou, 2021).

TNF-α contributes to the host's defense against infections caused by multi-microorganisms. Macrophages produce TNF-α, which is activated by several immune cells: NK cells, mast cells, T cell lymphocytes, and antigens. Because TNF-α is a potent pyrogen, it operates against leukocytes and endothelium and causes acute inflammation at low levels. It is frequently detected in the blood in circumstances of inflammation and infection. And due to the fact that TNF-α is cytotoxic, it induces pathological abnormalities in high levels of septic shock (Idrus *et al*., 2020).

Regarding the study of IL-35 levels in study population serum were higher in psoriatic patients without bacterial infections group (21.03) ng/ml compared with psoriatic patients with bacterial infections group (8.952) ng/ml and control groups (10.63) ng/ml. No significant differences between all groups as shown in (Figure 2).

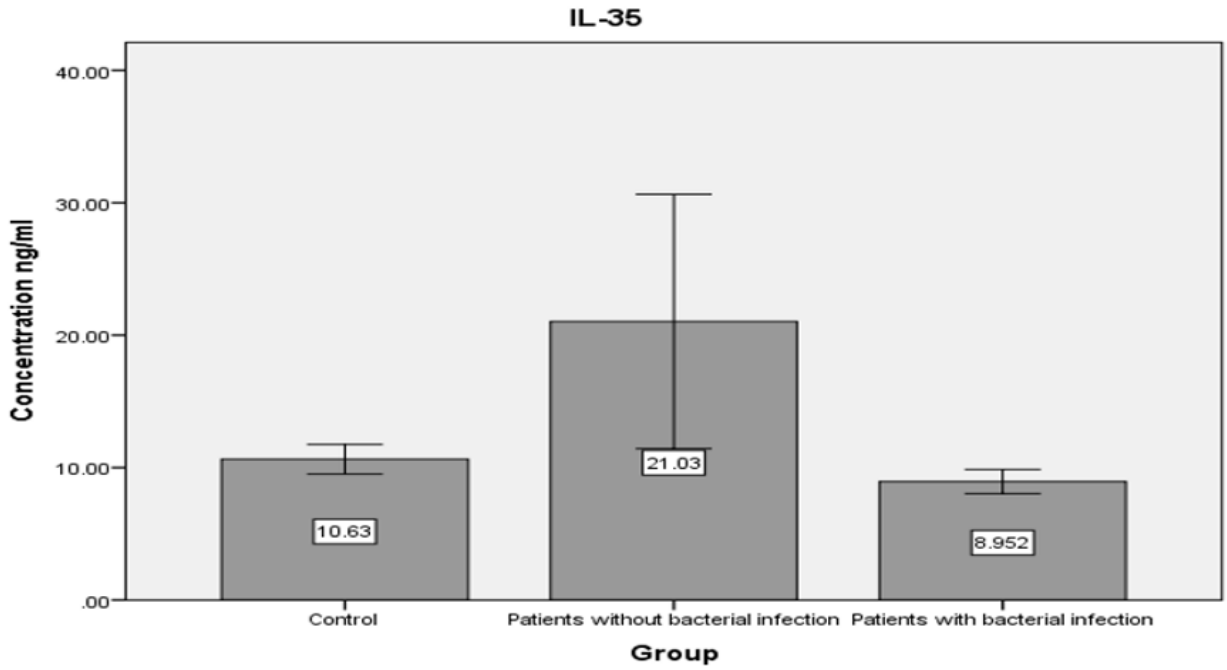

Figure 2: The Con. of IL- 35 in study population.

By attaching to its receptors and initiating further signaling pathways, IL-35 mediates immuno-signals and controls processes of several cells: T, B, macrophage, and dendritic cell development and function. Inflammatory autoimmune disorders have been found to express IL-35 abnormally. Furthermore, functional analysis revealed that serum levels of IL-35 are lower in psoriatic patients than in the control group, suggesting that IL-35 plays a crucial role in the development and start of these disorders (Ata Allah *et al*., 2024).

Agreement study by Owczarczyk-Saczonek *et al*., (2019) who demonstrated IL-35 levels were higher in psoriatic patients, with non-statistical significance. Other study carried out by Zhang *et al*., (2022), who observed that IL-35 expression in patients with psoriasis was significantly increased when compare with healthy group ($p = 0.0089$).

Contradictory study by Li *et al*., (2018) appeared IL-35 concentrations in plasma were decreased in psoriasis patients more than in healthy people ($P < .0001$).

Isolation of bacteria from the skin of psoriatic patients

The current study involved the collection of 50 psoriatic patients (14 with bacterial infections and 36 without bacterial infections). The results showed about 13 (26%) of Gram-positive bacteria and 1 (2%) of Gram-negative bacteria. The types of bacteria that observed in psoriatic lesion (Table 1). The most prevalent bacteria were *Staphylococcus aureus* 4 (8%), while lower rates were *Staphylococcus hominis* 1 (2%) and *Pantoea spp.* 1 (2%).

When destruction of the barrier occurs, it results in microbial dysbiosis, facilitates the entry of pathogenic microorganisms and subsequent inflammatory reactions, and triggers immunological activation, all of which exacerbate barrier damage (Margolis, 2022). Study by Quan *et al*., (2020) showed that the psoriasis people have a completely different cutaneous bacterial biota than healthy individuals, with a higher bacterial burden and less variety.

Table 1: Bacterial isolation from psoriatic group.

Bacterial Isolate	%	Gram stain	%
Staphylococcus aureus	8%	Gram positive	26%
Staphylococcus haemolyticus	6%		
Staphylococcus capitis	6%		
Staphylococcus epidermidis	4%		
Staphylococcus hominis	2%		
Pantoea spp.	2%	Gram negative	2%

CONCLUSION

The current study concluded that the levels of TNF-α and IL-35 were elevated in psoriatic patients compared to controls.

Ethical Approval

The research was proper accordance to the ethical standards established in the Declaration of Helsinki. Prior to sampling, consent was obtained from the patient or their partner. The research methodology, subject information, and permission form received approval from the College of Science, Kerbala University.

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