

Skin colonization of *Staphylococcus aureus* harboring superantigen toxin genes and its correlation with serum IL-22 level in psoriasis patients

Nancy Fouad¹, Fatma Mostafa¹, Marwa Soltan², Ali Zaki¹ and Rania A. Hassan¹

¹Department of Medical Microbiology & Immunology, Faculty of Medicine, Ain Shams University, Cairo, Egypt.

²Department of Dermatology & Andrology, Faculty of Medicine, Ain Shams University, Cairo, Egypt.

Corresponding author: Nancy Fouad, Department of Medical Microbiology & Immunology, Faculty of Medicine, Ain Shams University, Cairo, Egypt.
Email: nancyfouad@med.asu.edu.eg

Abstract

Psoriasis is a chronic debilitating skin disease with an estimated prevalence reaching 2% of the worldwide population. Psoriatic disease is driven by the interactions among innate and adaptive immune systems with structural components of the skin. Interleukin (IL)-22 mediates keratinocyte proliferation and epidermal hyperplasia, and changes in the structure of skin flora can play a role in the secretion of IL-22. The aim of this study was to correlate serum levels of IL-22 and *Staphylococcus aureus* toxins with disease activity in plaque psoriasis. The study group included 50 patients with mild, moderate, and severe psoriasis. The control group comprised 20 sex- and age-matched apparently healthy volunteers. IL-22 concentration was assessed in sera of patients and the control group by using the ELISA technique. The serum levels of IL-22 in patients were higher than in the control group, but the difference was statistically insignificant ($P=0.413$). Serum IL-22 levels were positively correlated with the Psoriasis Area and Severity Index (PASI) score of psoriasis patients ($P=0.0003$). The IL-22 serum levels in patients colonized with toxigenic strains of *S. aureus* were significantly higher than in patients colonized with non-toxigenic strains ($P=0.028$). In conclusion, IL-22 plays a role in the pathogenesis of psoriasis, and its secretion can be triggered by the toxins produced by *S. aureus* colonizing the skin of patients.

Keywords: Immune system, IL-22, Psoriasis, *S. aureus*, Superantigen.

Date received: 30 July 2022; **accepted:** 25 August 2022

Introduction

Psoriasis is an autoimmune skin disease characterized by the eruption of reddish, silvery-scaled patches. It affects 2 to 3% of the world population.¹ It is a systemic disease with a genetic component, associated with several other metabolic syndromes and systemic inflammatory diseases.² It is not a fatal disease,

yet it can have a bad impact on patients' quality of life.³ Psoriasis is associated with an inflammatory reaction mediated by impaired epidermal integrity, loss of immune tolerance to the cutaneous microbiome, and skin inflammatory response.⁴

A network of immune cells and their cytokines contribute to the pathogenesis of

psoriasis. Early in the disease, under certain conditions like microbial infections, keratinocytes produce antimicrobial peptides, such as β -defensins and cathelicidin (LL-37), which bind self-DNA from damaged cells and form an antigenic complex. Dendritic cells and plasmacytoid dendritic cells recognize this complex as a foreign antigen, then the cascade of cytokines starts eventually leading to the activation of the interleukin (IL)-23/T-helper 17 axis which is the cornerstone of psoriasis pathogenesis.⁵

IL-22 is one of the final products of the IL-23/T-helper 17 axis, responsible for immune homeostasis at barrier surfaces.⁶ IL-22 is a cytokine member of the IL-10 family produced by natural killer cells, $\gamma\delta$ T-cells, CD4+ T-cells, and Th22 cells, which are the main source of IL-22. Human dermal mastocytes can also secrete IL-22.⁷

IL-22 mediates its effects via the IL-22 receptor (IL-22R) complex. IL-22R is only expressed on the epidermal and mucosal cells; therefore, they are the targets for IL-22. The binding of IL-22 to its receptor complex leads to conformational changes in up-regulating genes responsible for cellular differentiation and epidermal hyperplasia, which is the hallmark of the pathology of psoriasis.⁸

Skin microbiome composition and its effect on psoriasis were investigated using both human and animal models, showing that psoriasis exacerbation can be related to epidermal or mucosal colonization with streptococci, *Malassezia*, *Staphylococcus aureus*, or *Candida albicans*.⁹

S. aureus is one of the commonest bacteria colonizing the skin in chronic dermatological diseases like atopic dermatitis and psoriasis.¹⁰ *S. aureus* mediates its pathologic effect on the skin by producing toxins among which are the superantigens, including *Staphylococcal enterotoxins* (SEs) [types A to V] and toxic shock syndrome toxin-1 (TSST-1).¹¹ SEs and TSST-1 induce polyclonal T-cells activation with a massive release of cytokines.^{1,12} In addition, they stimulate an isoform of corticosteroid receptor having an inhibitory effect, eventually leading to corticosteroid insensitivity. Therefore, the eradication of *S. aureus* may

enhance response to steroid therapy, which is the first line of treatment in psoriatic patients.¹³

Moreover, enterotoxins activate the signal transducer and activator of transcription (STAT3),¹⁴ $\gamma\delta$ T cells need STAT3 signals to proliferate and produce IL-17 and IL-22, which are responsible for the skin pathology in psoriasis.¹⁵ IL-22 is also crucial in the cutaneous immunity against *S. aureus* by promoting antimicrobial peptide gene expression. Therefore, heavy colonization with *S. aureus* leads to chronic IL-22 over-expression states causing pathologic effects. Targeting IL-22 and restoring the normal skin microbiome can be new strategies for psoriasis treatment.⁶

The present study aimed to evaluate the possible correlation between skin colonization with toxigenic strains of *S. aureus* (harboring genes of enterotoxins A, B and C and TSST-1) and serum levels of IL-22 in psoriasis patients.

Subjects and Methods

The study population

The study included 50 patients who attended Ain-Shams University Dermatology clinic, during the period from May 2021 to October 2021. Patients were clinically diagnosed according to the Psoriasis Area and Severity Index (PASI) score¹⁶. They were divided into 3 groups; group I comprised 10 patients with mild disease, group II comprised 20 patients with moderate disease, and group III comprised 20 patients with severe disease. Twenty apparently healthy volunteers matched by age and sex and with no family history of psoriasis were included as a normal control group.

Patients who had another autoimmune disease, systemic infection, or were on systemic treatment including glucocorticoids, immunosuppressive drugs, antibiotics (topical or systemic), or phototherapy, for one month before the study, were excluded.

Sample collection

For isolation of *S. aureus*, a skin swab was taken from both lesional and non-lesional skin of psoriatic patients and the skin of controls by using a sterile cotton swab. Sterile swabs were

immersed first in saline, and then in different lesions on the same patient.

For measuring IL-22 serum levels, 5 ml of venous blood were collected from each patient and control subject. Serum samples were separated by centrifugation at 600 xg and stored at -20°C until ELISA testing.

Skin swab culture and isolation of S. aureus

Skin swabs were cultured on blood agar and mannitol salt agar (MSA) (Oxoid™, UK) and incubated for 24 hours at 37 °C. *S. aureus* was isolated and identified using conventional microbiological methods according to Meylan et al., 2017.¹⁷ Isolates were inoculated on Mueller-

Hinton broth supplemented with 40% glycerol (Oxoid™, UK), and then stored at -80 °C until examined for toxin genes.

Detection of S. aureus toxins' genes by multiplex PCR

Multiplex PCR was used to detect the genes of *S. enterotoxins* A, B, C, TSST-1, using femA gene as an internal positive control. DNA extraction from *S. aureus* isolates was done by a commercial extraction kit (catalogue No.51304, QIAGEN®, Germany) according to the manufacturer's instructions. The primers' sequences used in the multiplex PCR are listed in Table 1.

Table 1. Sequences of used primers.

Gene	Primers' sequences (5'-3')	Location within Gene	Size of amplified product (bp)
<i>SEA</i>	GGTTATCAATGTGCGGGTGG	349-368	102
	CGGCACTTTTTCTCTTCGG	431-450	
<i>SEB</i>	GTATGGTGGTGTAACTGAGC	666-685	164
	CCAAATAGTGACGAGTTAGG	810-829	
<i>SEC</i>	AGATGAAGTAGTTGATGTGTATGG	432-455	451
	CACACTTTTAGAATCAACCG	863-882	
<i>TSST-1</i>	ACCCCTGTTCCCTTATCATC	88-107	326
	TTTTCAGTATTTGTAACGCC	394-113	
<i>fem-A</i>	AAAAAAGCACATAACAAGCG	1444-1463 1556-575	132
	GATAAAGAAGAAACCAGCAG		

The PCR reaction was carried out in a total volume of 50µL. The reaction contained 25µL of 2× Multiplex PCR Master Mix (Qiagen, Germany), 5µL of 10× primer mixture (0.2µM of each primer), and 0.5µL of DNA template. The final volume was adjusted to 50µL with RNase-free water (supplied with the kit). PCR amplifications were carried out according to Mehrotra et al., 2000,¹⁸ in a PTC1148 thermal cycler (BIO-RAD, Mexico). Initial denaturation was done at 95 °C for 15 min to activate the Hot-StartTaq polymerase, followed by 35 cycles of amplification, each included denaturation at 94 °C for 2 min, annealing at 57°C for 2 min, and extension at 72 °C for 1 min, with a final extension at 72 °C for 7 min.

Amplified PCR products were detected by electrophoresis on 1.5% agarose gel, stained

with ethidium bromide, and the results were visualized using an automated gel imaging instrument (Gel Doc™ EZ Imager, BIO-RAD, USA), Figure 1.

Detection of serum IL-22 levels using an ELISA technique

Serum IL-22 was measured using a commercial ELISA kit (catalog No: E-EL-H0106, Elabscience®, USA), according to the manufacturer's instructions. Plates were read and interpreted using an ELISA automated system (Lab system, Fenland).

Statistical analysis

Statistical analysis of the results was done using Statistical Package for the Social Sciences version 22. Quantitative data were expressed as

mean (\pm standard deviation, SD) or median and range as appropriate. Paired t-test was utilized

to determine the significance. A *P*-value of < 0.05 was considered statistically significant.

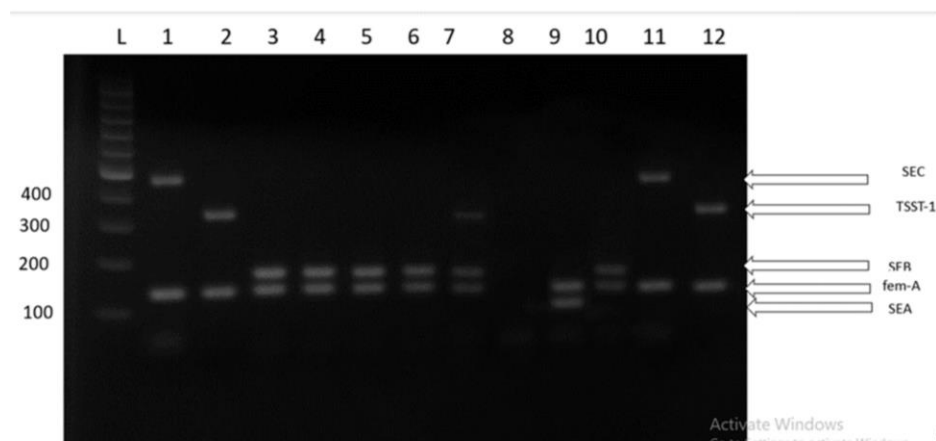


Figure 1. Multiplex PCR amplification products for the *Staphylococcus aureus* superantigen genes on agarose gel. L lane showing, 100-bp ladder; lanes 1–7, PCR amplicons of *S. aureus* isolates obtained from psoriasis cases; lanes 8–12 PCR amplicons of controls. Lanes: 1, SEC and femA; 2, TSST-1 and femA; lanes 3;4;5;6 SEB and femA; lane 7, TSST-1, SEB and femA; lane 8, negative control; lane 9, SEA and femA; lane 10, SEB and fem A; lane 11, SEC and femA; lane 12, TSST-1 and femA.

Results

Demographic data

The study included 50 patients, they were 28 males, and 22 females. Their ages ranged between 20 and 70 years, with a mean age of 41.2 ± 14 . The mean duration of the disease was 7.6 ± 9.14 years. The mean PASI score of the patients was 13 ± 7 .

Results of skin swab cultures

Of the 50 skin swabs taken from the lesional skin of the patients, 20 (40%) samples were positive for *S. aureus*. While of the 50 non-lesional skin swabs, 5 (10%) were positive for *S. aureus*. Only one (5%) of skin swabs from controls was positive for *S. aureus* colonization. The rate of *S. aureus* recovery was significantly different between the 3 sampled groups (Table 2).

Table 2. Distribution of *S. aureus* isolates in different isolation sites.

Origin of <i>S. aureus</i> isolates	<i>S. aureus</i> isolates, No. (%)	<i>P</i> -value
Normal controls (n=20)	1 (5.0%)	<0.0001
Non-lesional skin of patients (n=50)	5 (10%)	
Lesional skin of patients (n=50)	20 (40.0%)	

* $P \leq 0.05$ is significant.

Results of PCR detection of *S. aureus* toxins

Toxigenic strains of *S. aureus* were detected in 6 (12%) of the 50 psoriasis patients. While 14 (28%) of the 50 patients were colonized with

non-toxigenic strains of *S. aureus* and the rest of the patients 30 (60%) not colonized with *S. aureus* Figure (2).

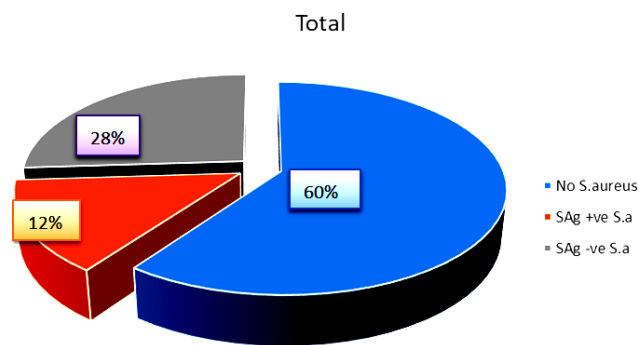


Figure 2. Distribution of toxigenic and non-toxigenic strains of *S. aureus* among the 50 studies patients. Of these, 14 (28%) patients were colonized with non-toxigenic strains of *S. aureus*, 6 (12%) colonized with toxigenic strains. The remaining 30 (60%) were not colonized with *S. aureus*.

Among the 20 *S. aureus* isolates obtained from the lesional skin of the patients, 6 (30%) were toxigenic. However, only one (20%) was toxigenic out of the 5 strains isolated from the non-lesional skin of the patients. The isolated

strain from the normal controls was negative for the tested toxins. No statistically significant difference was detected among the three groups ($P=0.746$) (Table 3).

Table 3. Origin of the different toxigenic *S. aureus* isolates.

Number of <i>S. aureus</i> isolated from different groups	Toxin-producing isolates No. (%)	<i>P</i> -value
Normal controls (n=1)	0 (0.0%)	NS
Non-lesional skin of patients (n= 5)	1 (20.0%)	
Lesional skin of patients (n= 20)	6 (30.0%)	
<i>P</i> > 0.05 is not significant (NS).		

Seven strains were toxigenic among the 25 *S. aureus* isolates obtained from both lesional and non lesional skin of the patients. One patient harbored *S. aureus* with SEB gene in both lesional and non-lesional skin. Among the 7 toxigenic *S. aureus* isolates, six showed only one type of toxin gene and, one strain was positive for both had SEB and TSST-1genes. The total number of *S. aureus* toxin genes were 8 among all isolates.

The most frequent toxin gene detected in *S. aureus* isolates was the SEB gene 62.5% (5/8

Toxins), followed by the genes for both TSST-1, 25% (2/8 Toxins) and SEC, 12.5% (1/8 Toxins). No isolates were positive for the SEA gene, Figure 3.

Correlation between the PASI score of patients and *S. aureus* colonization

The mean PASI score among patients colonized with *S. aureus* was 15.75 ± 6.58 , significantly higher than that of non-colonized patients (11.07 ± 7.32). ($P=0.025$) (Table 4).

Toxigenic strains

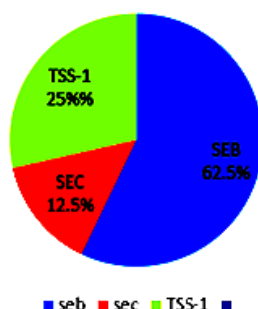


Figure 3. Percentages of different types of *S. aureus* toxins.

Table 4. Correlation between PASI score and *S. aureus* colonization

Group of patients	PASI score (mean ± SD)	P-value
Colonized with <i>S. aureus</i> (n= 20)	15.75 ± 6.58	0.025
Not colonized with <i>S. aureus</i> (n= 30)	11.07 ± 7.32	
P ≤ 0.05 is significant.		

The mean PASI score of psoriasis patients colonized with toxin-producing *S. aureus* was 20.33 \pm 8.7, significantly higher than that of

patients colonized with non-toxin producing isolates (13.7 \pm 4.5) ($P= 0.038$) (Table 5).

Table 5. Comparison of PASI score in patients colonized with toxigenic versus non-toxigenic *S. aureus* strains

Group of patients	PASI score	P-value
Colonized with toxigenic <i>S. aureus</i> (n= 6)	20.33 ± 8.71	0.038
Colonized with non-toxigenic <i>S. aureus</i> (n= 14)	13.79 ± 4.5	
<i>P</i> ≤ 0.05 is significant.		

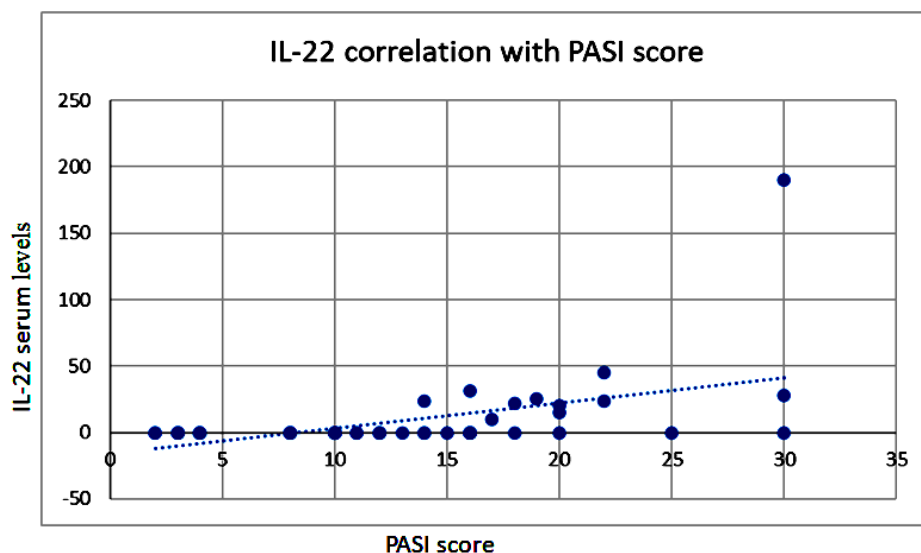
Serum IL-22 result

Data in Table 6 show that the mean serum level of IL-22 in the patients' group was 7.2 \pm 44.7 pg/ml, higher than that of the control group (3.16 \pm 7.5 pg/ml), however, the difference did

not reach statistical insignificance ($P=0.413$). However, there was a significant statistical correlation between PASI score and serum levels of IL-22 ($P= 0.0003$) (Figure 4).

Table 6. Comparison between IL- 22 serum levels in patients and control groups.

	Control No.= 20	Patients No.= 50	P-value
IL-22 level (mean \pm SD) (pg/ml)	3.16 \pm 7.5	7.2 \pm 44.7	NS
$P > 0.05$ is not significant (NS).			

**Figure 4.** Correlation of serum IL- 22 levels and PASI score of the patients.

Correlation between serum levels of IL-22 and *S. aureus* colonization

The mean serum IL-22 level of the 20 patients colonized with *S. aureus* (15.45 ± 42.67 pg/ml)

was higher than that of the 30 non-colonized patients with *S. aureus* (3.83 ± 8.7 pg/ml). However, the difference did not reach statistical significance ($P=0.153$) (Table 7)

Table 7. Comparison of the serum IL-22 levels between colonized and non-colonized patients with *S. aureus*

Group of patients	IL-22	P-value
Colonized with <i>S. aureus</i> No.= 20	15.45 ± 42.67 pg/ml	NS
Not colonized with <i>S. aureus</i> No.= 30	3.83 ± 8.7 pg/ml	

* $P \leq 0.05$ is significant.

Correlation between serum levels of IL-22 and colonization with toxigenic *S. aureus* strains

The mean serum level of IL-22 of the patients colonized with toxigenic strains of *S. aureus* was

46.5 ± 72.02 pg/ml, significantly higher than that of patients colonized with non-toxigenic *S. aureus* (2.14 ± 5.44 pg/ml) ($P= 0.028$) (Table 8 and Figure 5)

Table 8. Comparison of serum IL-22 levels between patients colonized with toxigenic strains of *S. aureus* and patients colonized with non-toxigenic strains of *S. aureus*.

Group of patients	IL-22	P-value
Colonized with toxigenic <i>S. aureus</i> (n= 6)	46.5 ± 72.02	0.028
Colonized with nontoxigenic <i>S. aureus</i> (n= 14)	2.14 ± 5.44	

* $P \leq 0.05$ is significant.

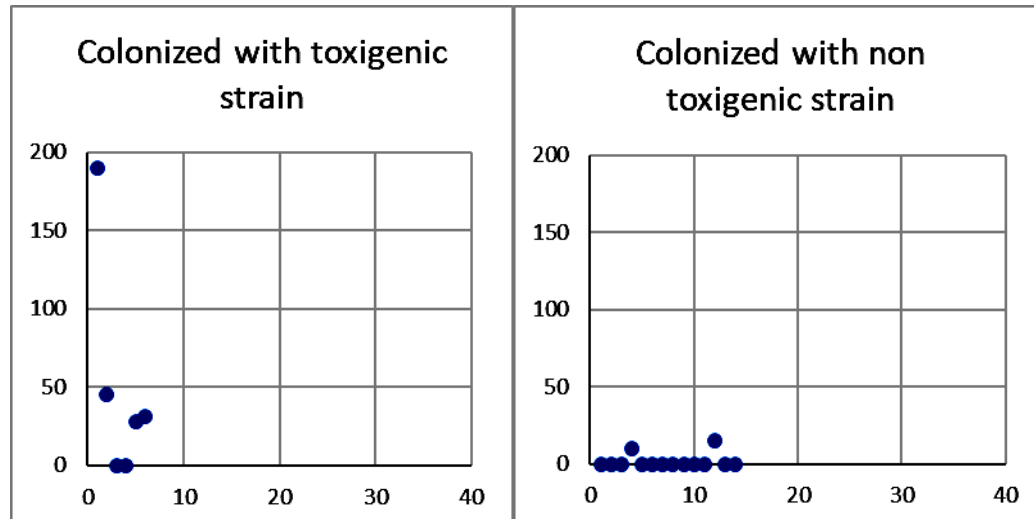


Figure 5. Dot plot graph. The left-side plot shows serum levels of IL-22 in patients colonized with toxigenic strains of *S. aureus* and the right-side plot shows serum levels of IL-22 in patients colonized with non-toxigenic strains of *S. aureus*.

Discussion

In the present study, we aimed to evaluate the possible correlation between skin colonization with toxigenic strains of *S. aureus* (harboring

genes of enterotoxins A, B, and C and TSST-1) and serum levels of IL-22 in psoriasis patients.

We found that 40% of psoriasis patients were colonized with *S. aureus* in their lesional

skin, while 10% of the patients harbored *S. aureus* in their healthy skin, and only 5% of the normal control subjects were colonized with *S. aureus*. There was a statistically significant difference between the number of *S. aureus* isolates recovered from psoriasis lesions, healthy skin of patients, and healthy skin of normal control subjects ($P < 0.001$). Our results were consistent with other studies who reported that *S. aureus* colonization rates ranged from 30% to 50%.^{10,19,20}

Higher percentages were reported in some other studies ranging from 60% to 80%²¹⁻²⁵, while, other different studies reported much lower rates of *S. aureus* skin colonization in psoriasis patients from 3% to 20%.^{26,27} In contrast to the above reports, in a study of *Elfatoiki et al.*, 2016, a higher rate of *S. aureus* colonization was reported in normal individuals' skin than in that psoriasis patients.²⁸ The variation in the prevalence of *S. aureus* and the presence of toxin genes in psoriasis patients among all the previous studies may be attributed to the intermittent colonization of psoriasis patients with *S. aureus* which is not always detected at the time of examination. Important factors of this discrepancy may possibly include the great variation in the clinical severity of psoriasis, different sampling sites, and the different sample size in each study.

Our results revealed a significant correlation between the severity of the disease, assessed using the PASI score, and *S. aureus* skin colonization ($P = 0.025$). These results were consistent with previous reports by Tomi et al., 2005²¹ and Balci et al., 2000²⁰ who found that the prevalence of *S. aureus* colonization in the lesional skin of patients with psoriasis was significantly correlated with disease severity.

Regarding the detection of *S. enterotoxins*, A, B, C, and TSST-1, we found that 6/20 (30%) of *S. aureus* isolates recovered from psoriatic patients' lesional skin were toxigenic. While among the 5 non-lesional skin isolates only one (20%) was toxigenic. The most frequently detected toxin among all isolates was SEB (62.5% of isolates). No statistically significant difference was detected comparing the percentage of toxigenic strains among the

isolation sites ($P = 0.746$). Similar results were reported by Tomi et al., 2005²¹ and Jassim et al., 2013,²⁴ they found that *S. aureus* isolates of lesional skin of plaque psoriasis patients were positive for enterotoxin genes detected by PCR. However, in contrast to our results, they reported a statistically significant difference in the number of enterotoxigenic *S. aureus* isolated from lesional and non-lesional skin of patients ($P < 0.01$).

Jassim et al., 2013²⁵ reported that of the lesional skin isolates they detected SEA and SEB genes were in 22.5% and 10%, respectively, and only one isolate from psoriatic healthy skin harbored SEB gene. In another study conducted by el Ferezli et al., 2008,²⁰ they detected SEA and SEC genes in 4 and 3, respectively out of 11 *S. aureus* isolates. Two of their isolates were positive for both genes. Similar to our results, none of their isolates from control subjects possessed enterotoxin genes.

In a study conducted by Atefi et al., 2012,²⁷ they isolated three *S. aureus* strains from 40 psoriasis patients and only one *S. aureus* isolate from 40 healthy control individuals. All four isolates were toxigenic. They reported a significant difference in TSST-1, enterotoxin A and enterotoxin C production between patients and controls ($P < 0.05$). Similarly, a study by Göçmen et al., 2015¹⁹ investigated the production of *S. enterotoxins* using PCR. Their results showed that six out of 26 strains isolated from skin carried enterotoxin genes. In agreement with our results, they also reported that the differences in numbers of toxigenic strains among isolation sites were statistically insignificant ($P = 0.135$).

Higher rates of toxigenic strains were reported by Balci et al., 2009.²¹ They investigated the genes of SEA, SEB, SEC, TSST-1, and exfoliative toxins (a and b). They detected toxins in 96.8% of *S. aureus* isolates in lesional skin and 42.3% of *S. aureus* isolates in non-lesional skin. Also, Atefi et al., 2014²⁹ measured *S. aureus* toxins in the sera of a group of psoriasis patients. TSST was detected in 47% (20/41) of cases, significantly higher than in controls 6% (1/28), ($P < 0.0001$). Also, enterotoxins (A, B, D) were detected in sera of

48.8% (21/41) of cases, significantly higher than in controls 6% (1/21), ($P<0.0001$).

We observed a correlation between PASI score and toxin production by *S. aureus*, similar results were reported by previous studies. In a study conducted by Tomi et al., 2005²² the presence of *S. aureus* isolates, and their toxins were statistically correlated to patients' PASI scores ($P=0.001$). Also, Göçmen et al., 2015¹⁹ found a positive correlation between toxin production and the PASI score of patients.

There are multiple lines of evidence supporting the concept that toxins play a role in the pathogenesis of psoriasis. Hauk et al., 2000¹³, studied the steroid action on the T-cells stimulated with *S. aureus* toxins including SEB, SEE, and TSST-1 compared to T-cells not stimulated with toxins. Their results revealed that the steroid action was hindered in the stimulated cells. They concluded that staphylococcal toxins could contribute to poor response to steroid treatment which was the core line of treatment in their psoriasis patients.

Normal skin barrier defense includes the secretion of IL-17 and IL-22 which are important for the recruitment of neutrophils and for defense against *S. aureus*.³⁰ A study by Van Belle et al., 2012³¹ found that IL-22 was important to maintain psoriasiform skin inflammation in a mouse model where the scaly skin lesions were absent in IL-22-deficient mice.

In the present study, IL-22 serum levels were higher in psoriasis patients (7.2 ± 44.7 pg/ml) than in the control group (3.00 ± 7.33 pg/ml), however, the difference did not reach statistical significance ($P=0.413$). In agreement with the results of the present study, a study of Sobhan et al., 2016³² reported a non-significant elevation of serum levels of IL-22 in a group of psoriasis patients when compared to controls. On the other hand, several studies found a statistically significant difference between psoriasis patients and their control groups.^{4,33–36} The discrepancy between the levels of IL-22 in various studies can be explained by the fact that IL-22 is produced and acts mainly locally, and therefore plasma levels might be lower than in the inflammatory area. Other explanations may be that *S. aureus* could trigger different cytokines other than IL-22 or the

ability of *S. aureus* to have a direct inflammatory effect on the skin through its virulence factors without triggering an immunologic process.

Our results revealed that IL-22 serum levels were positively correlated to the PASI score of patients ($P<0.001$). Similar to these results, many studies reported positive correlation between PASI score of patients and the serum levels of IL-22.^{33–36} However, in contrast to the previous studies, some other studies found no statistically significant correlation between IL-22 levels and PASI scores in their studied groups^{32,37,38}

In our study, we found no statistically significant difference in IL-22 serum levels between the psoriasis patients colonized with *S. aureus* compared to the non-colonized patients ($P=0.153$). However, among the group of patients colonized with *S. aureus*, IL-22 was significantly elevated in patients harboring toxigenic strains of *S. aureus* than those having non-toxigenic strains ($P=0.028$). In consistence with our findings, Wawrzycki et al., 2019.⁴ and Niebuhr et al., 2014,³⁹ conducted in vitro studies on T-cells isolated from psoriasis. They measured the level of IL-22 produced by T-cells which was higher after stimulation with SEB. This may prove the role of SEB in the production of IL-22.

Finally, our results should be interpreted with caution as there is uncertainty about whether IL-22 is a pro-inflammatory or a protective cytokine.⁴⁰ Further investigations are required to confirm the possibly protective or harmful effects of IL-22 in the 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 the immunopathogenesis of psoriasis.

In conclusion, the results of the present study suggested a role of *S. aureus* colonization in the immunopathogenesis of psoriasis. *Staphylococcal* toxins may trigger the production of IL-22 in psoriasis patients.

Author Contributions

All authors listed have contributed equally to the work and approved it for publication.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) denies receipt of any financial support for the research, authorship, and/or publication of this article.

Ethical approval

The study protocol was reviewed and approved by the Research Ethics Committee of the Faculty of Medicine-Ain Shams University (No. FMASU M D 94/2020).

Informed consent

A signed consent form was obtained from each study participant.

References

1. Yarwood, J. M.; Leung, D. Y. M.; Schlievert, P. M. (2000). Evidence for the Involvement of Bacterial Superantigens in Psoriasis, Atopic Dermatitis, and Kawasaki Syndrome. *FEMS Microbiology Letters*, 192 (1), 1–7. [https://doi.org/10.1016/S0378-1097\(00\)00400-6](https://doi.org/10.1016/S0378-1097(00)00400-6).
2. de Oliveira, P.; Cardoso, R.; De Andrade Lima, E. et al (2015). Plaque-Type Psoriasis in Brazilian Patients. *Mediators of Inflammation*, 2015, 1–6.
3. Johnston, A.; Gudjonsson, J. E. (2014). 22 Again: IL-22 as a Risk Gene and Important Mediator in Psoriasis. *Journal of Investigative Dermatology*, 134 (6), 1501–1503. <https://doi.org/10.1038/jid.2014.81>.
4. Wawrzycki, B.; Pietrzak, A.; Grywalska, E. et al (2019). Interleukin-22 and Its Correlation with Disease Activity in Plaque Psoriasis. *Archivum Immunologiae et Therapiae Experimentalis*, 67, 103–108. <https://doi.org/10.1007/s00005-018-0527-5>.
5. Di Nardo, A.; Braff, M. H.; Taylor, K. R. et al (2007). Cathelicidin Antimicrobial Peptides Block Dendritic Cell TLR4 Activation and Allergic Contact Sensitization. *The Journal of Immunology*, 178 (3), 1829–1834. <https://doi.org/10.4049/jimmunol.178.3.1829>.
6. Zhu, C.; Fei, W.; Wang, W. et al (2021). Copy Number Variation Analysis of IL22 and LCE3C in Different Subtypes of Psoriasis in a Chinese Han Population. *Medical Science Monitor* 2021, 27, 1–8. <https://doi.org/10.12659/msm.934927>.
7. Niebuhr, M.; Scharonow, H.; Gathmann, M. et al (2010). Staphylococcal Exotoxins Are Strong Inducers of IL-22: A Potential Role in Atopic Dermatitis. *Journal of Allergy and Clinical Immunology*, 126 (6), 1176–1183.e4. <https://doi.org/10.1016/j.jaci.2010.07.041>.
8. Guttman-Yassky, E.; Brunner, P. M.; Neumann, A. U. et al (2018). Efficacy and Safety of Fezakinumab (an IL-22 Monoclonal Antibody) in Adults with Moderate-to-Severe Atopic Dermatitis Inadequately Controlled by Conventional Treatments: A Randomized, Double-Blind, Phase 2a Trial. *Journal of the American Academy of Dermatology*, 78 (5), 872–881.e6. <https://doi.org/10.1016/j.jaad.2018.01.016>.
9. Gupta, M.; Weinberg, J. M.; Yamauchi, P. S. et al (2021). Psoriasis : Embarking a Dynamic Shift in the Skin Microbiota. No. May, 1–5. <https://doi.org/10.1111/jocd.14273>.
10. Zuel-fakkar, N. M. Study of Erythroderma and Psoriasis Exacerbation by Staphylococcal Superantigens. 2010, 123–128.
11. Yarwood, J. M.; Leung, D. Y. M.; Schlievert, P. M. (2000). *Evidence for the Involvement of Bacterial Superantigens in Psoriasis, Atopic Dermatitis, and Kawasaki Syndrome*. <https://doi.org/10.1111/j.1574-6968.2000.tb09350.x>.
12. Ortega, E.; Abriouel, H.; Lucas, R. et al (2010). Multiple Roles of *Staphylococcus Aureus* Enterotoxins: Pathogenicity, Superantigenic Activity, and Correlation to Antibiotic Resistance. *Toxins*, 2 (8), 2117. <https://doi.org/10.3390/TOXINS2082117>.
13. Hauk, P. J.; Hamid, Q. A.; George, P. (2000). Induction of Corticosteroid Insensitivity in Human PBMCs by Microbial Superantigens. 2000, 782–787. <https://doi.org/10.1067/mai.2000.105807>.
14. Willerslev-Olsen, A.; Krejsgaard, T.; Lindahl, L. M. et al (2016). Staphylococcal Enterotoxin A (SEA) Stimulates STAT3 Activation and IL-17 Expression in Cutaneous T-Cell Lymphoma. *Blood*, 127 (10), 1287–1296. <https://doi.org/10.1182/blood-2015-08-662353>.
15. Agerholm, R.; Rizk, J.; Viñals, M. T. et al (2019). STAT3 but Not STAT4 Is Critical for $\gamma\delta$ T17 Cell Responses and Skin Inflammation. *EMBO reports* 20 (11). <https://doi.org/10.15252/embr.201948647>.

16. Raychaudhuri, S. K.; Maverakis, E.; Raychaudhuri, S. P. (2014). Diagnosis and Classification of Psoriasis. *Autoimmunity Reviews*, 13 (4–5), 490–495. <https://doi.org/10.1016/J.AUTREV.2014.01.008>.
17. Meylan, P.; Lang, C.; Mermoud, S.; J. et al (2017). Skin Colonization by *Staphylococcus aureus* Precedes the Clinical Diagnosis of Atopic Dermatitis in Infancy. *Journal of Investigative Dermatology* 2017, 137 (12), 2497–2504. <https://doi.org/10.1016/J.JID.2017.07.834>.
18. Mehrotra, M.; Wang, G.; Johnson, W. M. (2000). Multiplex PCR for Detection of Genes for *Staphylococcus Aureus* Enterotoxins, Exfoliative Toxins, Toxic Shock Syndrome Toxin 1, and Methicillin Resistance A Multiplex PCR Assay for Detection of Genes for Staphylococcal Enterotoxins A to E (EntA, EntB, EntC, EntD, and EntE), Toxic Shock Syndrome Toxin 1 (Tst), Exfoliative Toxins A and B (EtaA and EtaB); 2000; Vol. 38.
19. Göçmen, J. S.; Şahiner, N.; Koçak, M. et al (2015). PCR Investigation of Pantone-Valentine Leukocidin, Enterotoxin, Exfoliative Toxin, and Agr Genes in *Staphylococcus aureus* Strains Isolated from Psoriasis Patients. *Turkish Journal of Medical Sciences*, 45 (6), 1345–1352. <https://doi.org/10.3906/sag-1408-54>.
20. El Ferezli, J.; Jenbazian, L.; Rubeiz, N. et al (2008). M. Streptococcus Sp. and *Staphylococcus aureus* Isolates from Patients with Psoriasis Possess Genes That Code for Toxins (Superantigens): Clinical and Therapeutic Implications. *Immunopharmacology and Immunotoxicology*, 30 (2), 195–205. <https://doi.org/10.1080/08923970801946808>.
21. Balci, D. D.; Duran, N.; Ozer, B. et al (2009). High Prevalence of *Staphylococcus aureus* Cultivation and Superantigen Production in Patients with Psoriasis. *European Journal of Dermatology* 2009, 19 (3), 238–242. <https://doi.org/10.1684/ejd.2009.0663>.
22. Tomi, N. S.; Kränke, B.; Aberer, E. (2005). Staphylococcal Toxins in Patients with Psoriasis, Atopic Dermatitis, and Erythroderma, and in Healthy Control Subjects. *Journal of the American Academy of Dermatology* 2005, 53 (1), 67–72. <https://doi.org/10.1016/J.JAAD.2005.02.034>.
23. Marcus, E.; Demmler, D.; Rudolph, A. et al (2011). Bacterial Colonization of Psoriasis Plaques. Is It Relevant? <https://doi.org/10.4081/dr.2011.e14>.
24. Abbas, E. C.; Al-mohana, A. M.; Al-Dhalimi, M. A. et al (2016). Cytokine Serum Level Association with Superantigen Production by *Staphylococcus aureus* in Psoriasis Vulgaris. *Research Journal of Pharmaceutical, Biological and Chemical Sciences*, 7 (4), 172–180.
25. Jassim, H. a; Bakir, S. S.; Alhamdi, K. I. et al (2013). Polymerase Chain Reaction (PCR) for Detection Superantigenicity of *Staphylococcus aureus* Isolated from Psoriatic Patients. 1 (1), 22–27.
26. ALY, R.; MAIBACH, H. I.; MANDEL, A. (1976). Bacterial Flora in Psoriasis. *The British journal of dermatology*, 95 (6), 603–606. <https://doi.org/10.1111/J.1365-2133.1976.TB07031.X>.
27. Atefi, N.; Tabaie, M.; Noorbakhsh, S. et al (2012). The Role of Staphylococcus Superantigens in Chronic Plaque Type Psoriasis. *Iranian Journal of Dermatology*, 15 (59), 1–3.
28. Zahra Elfatoiki, F.; Azhari, M. El; Kettani, A. El et al (2016). Psoriasis and *Staphylococcus aureus* Skin Colonization in Moroccan Patients Case Series Open Access. *Pan African Medical Journal-ISSN*, 23, 1937–8688. <https://doi.org/10.11604/pamj.2016.23.33.7198>.
29. Atefi, N.; Noorbakhsh, Samileh; Sahar, Darestani, G. et al (2014). The Rise of Staphylococcal Super Antigens in Psoriatic Patients: A Case-Control Study. *Jundishapur J Microbiol*, 7 (5), 9912. <https://doi.org/10.5812/jjm.9912>.
30. Malhotra, N.; Yoon, J.; Leyva-Castillo, J. M. et al (2016). IL-22 Derived from $\gamma\delta$ T Cells Restricts *Staphylococcus aureus* Infection of Mechanically Injured Skin. *Journal of Allergy and Clinical Immunology*, 138 (4), 1098–1107.e3. <https://doi.org/10.1016/j.jaci.2016.07.001>.
31. Van Belle, A. B.; de Heusch, M.; Lemaire, M. M. et al (2012). L. IL-22 Is Required for Imiquimod-Induced Psoriasiform Skin Inflammation in Mice. *The Journal of Immunology*, 188 (1), 462–469. <https://doi.org/10.4049/jimmunol.1102224>.
32. Sobhan, M. R.; Farshchian, M.; Hoseinzadeh, A. et al (2016). Serum Levels of IL-10 and IL-22 Cytokines in Patients with Psoriasis. *Iranian Journal of Immunology*, 13 (4), 317–323. <https://doi.org/10.1111/IJlv13i4A8>.
33. Hofny, E. M.; Morsy, H.; Hasaball, A. et al (2017). Serum Level of Interleukin-22 in Patients with Psoriasis and Its Correlation with Disease Severity. *Journal of Current Medical Research and Practice*, 2 (2), 133. https://doi.org/10.4103/jcmrp.jcmrp_27_16.
34. Michalak-Stoma, A.; Bartosińska, J.; Kowal, M. et al (2013). Serum Levels of Selected Th17 and Th22 Cytokines in Psoriatic Patients. *Disease Markers*, 35 (6), 625–631. <https://doi.org/10.1155/2013/856056>.

35. Kagami, S.; Rizzo, H. L.; Lee, J. J. et al (2010). Circulating Th17, Th22, and Th1 Cells Are Increased in Psoriasis. <https://doi.org/10.1038/jid.2009.399>.
36. Liu, X. Y.; Zhao, Y.; Zhang, H.; et al (2020). Comparison between Guttate and Plaque Psoriasis in Terms of Serum Inflammatory Cytokines and Antimicrobial Peptides. *Chinese Medical Journal*, 133 (24), 3004–3006. <https://doi.org/10.1097/CM9.0000000000001227>.
37. Caproni, M.; Antiga, E.; Melani, L. et al (2008). Serum Levels of IL-17 and IL-22 Are Reduced by Etanercept, but Not by Acitretin, in Patients with Psoriasis: A Randomized-Controlled Trial. <https://doi.org/10.1007/s10875-008-9233-0>.
38. Boniface, K.; Guignouard, E.; Pedretti, N. et al (2007). Role for T Cell-Derived Interleukin 22 in Psoriatic Skin Inflammation. *Clinical and Experimental Immunology* 2007, 150 (3), 407–415. <https://doi.org/10.1111/j.1365-2249.2007.03511.x>.
39. Niebuhr, M.; Mainardy, J.; Heratizadeh, A. et al (2014). Staphylococcal Exotoxins Induce Interleukin 22 in Human Th22 Cells. *International Archives of Allergy and Immunology*, 165 (1), 35–39. <https://doi.org/10.1159/000367923>.
40. Dudakov, J. A.; Hanash, A. M.; Van Den Brink, M. R. M. (2015). Interleukin-22: Immunobiology and Pathology. <https://doi.org/10.1146/annurev-immunol-032414-112123>.