Expression Analysis of CCL27: A Sensitive biomarker in distinguishing between psoriasis and atopic dermatitis

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ABSTRACT

Background and objective: Eczema and psoriasis are heterogeneous cutaneous inflammatory disorders with broad and occasionally overlapping diagnostic criteria, making it difficult to distinguish psoriasis from eczema. Despite the reality that potential biomarkers, such as CCL27, have been identified for differentiating psoriasis and eczema. The current study's goals included determining the association between CCL27 expression level and disease severity and evaluating the expression level of CCL27 as a biomarker for distinguishing psoriasis and atopic dermatitis.
Methodology: A case-control study was carried out on 100 patients (50 with psoriasis and 50 with atopic dermatitis), and 50 age- and sex-matched controls were recruited after verbal and written consent was obtained. Patients receiving local or systemic treatment or with an inflammatory skin disorder were excluded. Reverse transcriptase-quantitative polymerase chain reaction (RT-qPCR) was used to evaluate the CCL27 expression level.
Results: Our study found a highly significant increase in CCL27 expression (P<0.00001) in eczema patients compared to psoriasis and healthy control groups. To detect eczema, CCL27 expression levels with a cut-off value of 5.39-fold change had a high sensitivity (91.2%) and specificity (100%). In eczema patients, CCL27 was positively correlated with disease severity using SCORing Atopic Dermatitis scores (SCORAD) (P<0.00001). On the other hand, a negative correlation between CCL27 and psoriasis severity scoring using Psoriasis Area and Severity Index (PASI).
Conclusion: We conclude that CCL27 is a sensitive biomarker in differentiating psoriasis from eczema and positively correlates with psoriasis severity. A future prospective large-scale study is recommended to support our findings.

Keywords: *Psoriasis, Atopic Dermatitis, CCL27, Molecular Biomarkers*

1. INTRODUCTION

Skin disorders can result in significant disability. In addition to itching and pain, skin disorders can physically disfigure an individual. Despite generally low mortality rates, skin disorders frequently result in a lower quality of life for patients. With 1.79% of the overall global disease burden measured in disability-adjusted life years (DALYs), skin disease was the fourth most common non-fatal disease burden (Hay *et al*., 2014). Atopic dermatitis (AD) and psoriasis (PS) are frequent, chronic inflammatory skin disorders. Despite their differences, AD and PS have several characteristics in common,

including the migration of immune cells into the skin, increased expression of particular cytokines that cause inflammation, and changes to the skin's protective barrier (Guttman-Yassky *et al.,* 2018). Even though PS and AD have different pathophysiology, it has been demonstrated that PS is associated with both atopy and AD (Guttman-Yassky & Krueger, 2017). Although PS can exhibit eczematous changes in the acute stage, AD can exhibit psoriasis from lichenified alterations in the persistent/resistant stage. It is possible to confuse AD and PS for the existence of two distinct diseases (Docampo *et al.,* 2019).

A tissue-specific T cell-homing chemokine that targets the skin has been identified. C-C motif chemokine ligand 27, also known as ESkine, ALP, ILC, or ILR locus chemokine, was first identified as the cutaneous T cell-attracting chemokine. When there is inflammation, keratinocytes in the skin produce CCL27 specifically, which mediates the adhesion and homing of T cells that infiltrate the skin (Lopes-Marques *et al.,* 2019). Both atopic and psoriatic skin have been shown to have increased CCL27 expression (Riis *et al.,* 2011; Garzorz & Eyerich, 2015). Patients with psoriasis from dermatitis may benefit from more accurate treatment and diagnosis as a result of the use of CCL27 as a biomarker to consistently differentiate between AD and PS (Quaranta *et al.,* 2014; Garzorz-Stark *et al.,* 2016; He *et al.,* 2021; Renert-Yuval *et al.,* 2021). Compared to AD and normal skin, psoriatic skin's CCL27 mRNA dramatically decreased (Nomura *et al.,* 2003). Clinical research, however, revealed that CCL27 is significantly reduced in the lesional skin of psoriasis patients (Li *et al.,* 2021).

Therefore, this study aimed to examine CCL27 expression to differentiate between atopic dermatitis and psoriasis and to establish its correlation to disease activity and severity.

2. PATIENTS AND METHODS

2.1. Design and Population

This study was designed to determine the molecular markers to differentiate between psoriasis and eczema. Each participant was provided with an informed verbal idea and gave written consent about the research. In its regular meeting, this study was accepted by the Faculty of Medicine, Menofia University's ethics approval committee. Participants were divided into three groups as follows: group 1 consisted of 50 patients with psoriasis who had been clinically diagnosed and evaluated; group 2 comprised 50 patients with atopic dermatitis; and group 3 consisted of 50 healthy volunteers who were matched for age and sex and served as the control group. The patients' diagnoses were made for the first time at the Dermatology Outpatient Clinic without any medical history. The practical aspects of this study were carried out at the Department of Molecular diagnostics and therapeutics, GEBRI, University of Sadat City, Molecular diagnostics, therapeutics, and genomics lab. Patients underwent a general and local examination and an in-depth review of their personal, recent, and family histories. Clinical criteria previously published were used to diagnose (Eyerich *et al.,* 2011). Using the PASI (Psoriasis Area and Severity Index), EASI (Eczema Area and Severity Index), and SCORing Atopic Dermatitis (SCORAD), the patient's clinical condition was evaluated. The following cases were selected and included in the study: adult patients with newly diagnosed psoriasis and eczema who were not on systemic medications (ages 18 to 60). Patients with multiple sclerosis, autoimmune diseases, endocrine disorders, dermatological conditions other than plaque psoriasis, and those on systemic steroids, methotrexate, biological therapy, or any other

systemic drugs were excluded from this study.

2.2. Laboratory investigations

Five ml venous blood samples were obtained through sterile venipuncture without foaming. Each sample was divided into two parts. The first part was put into sterile vacutainer tubes containing Ethylene diamine tetra acetic acid (EDTA) for total RNA extraction and complete blood count (CBC) using an automated hematology analyzer (Pentra 80). The second part was centrifuged at 1500 rpm for 10 minutes to separate serum samples for liver and kidney functions using the Cobas 6000 analyzer (c 501 modules).

2.3. Isolation of total RNA

Until total RNA was isolated using the MagNA Pure Compact Nucleic Acid Isolation Kit I (Cat. No. 03 730 964 001), according to the manufacturer's instructions, blood samples were kept at -80°C. A NanoDrop ND-1000 spectrophotometer was used to assess the quantity and quality of RNA (Thermo Fisher Scientific, Inc.). RNA purity was determined by comparing the 260/280 nm and 260/230 nm absorbance ratios (Farhat, 2012).

2.4. Quantification of CCL27 gene expression levels

Complementary DNA (cDNA) was synthesized by RT-qPCR and was performed using Thermo Fisher TaqMan Low-Density Array cards (RT-qPCR). (Thermo Fisher, Waltham, and Mass). A mixture of 1 µl of reverse transcriptase enzyme, 4 µl of 5x TransAmp buffer, and 5 µl of RNase-free water was added to 10 µl of RNA extract. The reverse transcriptase enzyme was stopped using an Applied Biosystems 2720 Thermal Cycler, ALT, USA (Bioline, USA) for a single cycle that lasted 10 minutes at 85 ℃, 15 minutes at 42 ° C, and finally 5 minutes at 85 ° C. The primer design tool Primer-BLAST from NCBI was used to create primers and hydrolysis probes for the targeted amplification of the CCL27 gene and the internal control GAPDH gene (https://www.ncbi.nlm.nih.gov/tools/primer blast/). Primer and probe sequences were as follows (forward, reverse and probe): 5'-TGCATCCACCCTCAGAAT-3', 5'-TTCCTTGTCAGCCCCAAA-3', 5'-GGGACTCTACCTAACCTG-3' for CCL27 gene and 5'- CTGGAGAAAGCTGCCAAA-3', 5'- TGTTGAAGTCACAGGAGA-3' and 5'-AGAAGGTAGTGAAGCAG-3' for GAPDH (reference gene). The reactions were performed as 40 cycles of denaturation at 95 °C for 15 s, annealing at 58 °C for 30 s, and extension at 72 °C for 30 s, with a final stage of denaturation at 95 °C for 15 s, annealing at 60 °C for 1 min, and denaturation at 95 °C for 15 s (real-time PCR handbook, life-technologies; qPCR for mRNA quantitation: future-science.com). The number of cycles needed for the amplicon concentration to cross the threshold in real-time PCR is known as the cycle threshold (CT). The relative expression levels of CCL27 over GAPDH (housekeeping reference gene) were determined using the equation $2^{(-\Delta\Delta CT)}$ method (Livak & Schmittgen, 2001).

2.5. Statistical analysis

Utilizing SPSS (Statistical Package for Social Sciences) version 28 for Windows®, the gathered data were coded, processed, and analyzed (IBM SPSS Inc, Chicago, IL, USA). Frequency distributions and relative percentages were used to display qualitative data. The mean SD format was used to express quantitative data (Standard deviation). Statistical significance was

determined using two-tailed P values ($p<0.05$). To differentiate between psoriasis and eczema, the Receiver Operating Curve (ROC) test was used to calculate the diagnostic indices (sensitivity, specificity, positive and negative predictive values, and accuracy) for CCL27.

3. RESULTS

3.1. Demographic, biochemical, and clinical characteristics of study subjects

Table 1 summarizes the study participants' demographic, biochemical, and clinical characteristics. During the study period, 100 patients were recruited, of which 50 had psoriasis (20 men, 30 women; mean age 39.6 ± 15.4 years) and 50 had eczema (37 men, 13 women; mean age 31.0 ± 13.8 years). A control group of 50 healthy subjects (27 men, 23 women; mean age 37.3 ± 15.7 years) was included for comparison. No significant difference in age, gender, smoking status, or family history was observed among the three groups, as well as other parameters such as ALT, AST, bilirubin, creatinine, urea, hemoglobin, total leucocyte count, and platelets. While the disease duration and scoring showed a highly significant variation among all studied groups ($P < 0.0001$).

3.2. Blood relative expression of CCL27 and distinguishing between psoriasis and eczema

The expression levels of CCL27 in the blood of all studied groups were assessed using RT-qPCR analysis. The highest value was in patients with psoriasis, with a significant difference. Data explaining the expression level of CCL27 is shown in Table 2. In terms of psoriasis and eczema severity, the level considerably rises as the disease progresses. Statistical analysis of the mean CCL27 expression level in the patients with psoriasis versus the mean PASI score indicated a statistically significant decrease in the CCL27 level as the PASI score increased, while in patients with eczema versus the mean SCORAD score indicated a statistically significant increase in the CCL27 level as the SCORAD score increased as shown in Table 3.

3.3. Receiver Operating Characteristic (ROC) of the CCL27

Receiver operator characteristic (ROC) curve analysis was used to determine the cut-off value for CCL27 expression level to distinguish between psoriasis and eczema (Figure 1). The ROC curve's results showed that patients with eczema had the highest area under the curve (AUC) value (0.833). At a cut-off value of 5.39, CCL27 showed 91.2 % sensitivity and 100% specificity. CCL27 could be used to differentiate the two disease conditions (psoriasis and eczema) ($P<0.018$).

4. DISCUSSION

Common inflammatory skin conditions with unique clinical symptoms include psoriasis and atopic dermatitis (Barry *et al.,* 2021). Both diseases share similar pathological alterations, immunological mechanisms, genetic profiles, and comorbidities (Bronckers *et al.,* 2015; Kirsten *et al.,* 2021). Lack of knowledge or the absence of typical lesions could be the cause. Even dermatologists may occasionally struggle to distinguish between two cases of what is known as "psoriasis eczema," which in 20% of cases included both disease's symptoms (PsEma) (Barry *et al.,* 2021). This study aimed to estimate the expression level of CCL27 in patients with psoriasis and eczema, compares them with normal individuals to distinguish between psoriasis and eczema, and correlate them with the severity of the disease.

The present study reported the demographic and clinical data of study individuals as exposure to psoriasis and atopic dermatitis. The age of all study populations ranged from 18 to 60 years, with a mean of 36.6± 14.9 years. The mean age at presentation of psoriasis patients was 39.6 ± 15.4 years, while the mean age for atopic dermatitis was 31.0 ± 13.8 compared with the healthy control group (37.3 ± 15.7). The patients with psoriasis were older than those with eczema, and the variation in age between all studied groups was statically non-significant. This study finding was in agreement with previous studies, which reported that all ages could be affected by eczema and psoriasis, but eczema often first manifests in infants and children, whereas psoriasis typically always does at a later age (Abo-Zaid *et al.,* 2018; Bozek *et al.,* 2020). In the current study, the prevalence of psoriasis was higher in females than males, 30/20 with a ratio of 1.5:1. This finding was in line with previous studies that showed females had a higher prevalence of psoriasis (Tsai *et al.,* 2011; Egeberg *et al.,* 2017; Murer *et al.,* 2021). However, in other studies, there was no difference in the prevalence of psoriasis between the sexes (Parisi *et al.,* 2013; Armstrong *et al.,* 2021). In contrast, the prevalence of eczema was higher in males than females 37/13 with a ratio of 2.85:1. This finding was in agreement with a previous study, which demonstrated a higher prevalence of eczema in males (de Lusignan *et al.,* 2021). Another study showed the opposite, with the female population having a higher prevalence (Arnedo-Pena *et al.,* 2020). The difference in the disease prevalence according to gender was not statically significant (P>0.05). In this study, the majority of participants (81.34%) were non-smokers. Between "smokers" and "non-smokers," there were no significant variations in the prevalence of psoriasis and eczema. The prevalence of psoriasis and eczema according to smoking status were (34%, and 12%, respectively). In agreement with previous studies, smoking contributes to psoriasis and eczema severity without significantly affecting the disease prevalence (Cataldo *et al.,* 2014; Naldi, 2016).

In this study, the prevalence of psoriasis and eczema is similar in the participants with or without a family history. There was no significant difference between the effect of the history of diseases. This was in contrast to previous studies, which reported that a family history of psoriasis was associated with earlier psoriasis onset and enthesitis, and that eczema in the index child was significantly associated with eczema in mothers as fathers (Saunes *et al.,* 2011; Solmaz *et al.,* 2020). In this study, the average disease duration in the psoriasis group was 15.5 ± 16.3 months, while the mean atopic dermatitis duration was longer than psoriasis, 106.6 ± 13.8 months. The difference in the disease duration showed that eczema takes more time than psoriasis. This result agreed with the previous report showing that the eczema duration was longer than psoriasis. To evaluate the clinical severity and track therapy effectiveness in psoriasis and atopic dermatitis, PASI, EASI, and SCORAD index were used as well-respected scoring systems (Yamamah *et al.,* 2012; Bang *et al.,* 2021). In the current study, regarding the disease severity, the scoring of both psoriasis and eczema were evaluated using (PSAI, ESAI, and SCORAD), and the mean values of all studied scoring tools were (8.7±1.2, 12·8± 9·82, 45.6±14.05) respectively. There was a highly significant variation between the mean scores for all groups (P < 0.0001). The results of the present study revealed that in both psoriasis and eczema, there was no significant association with all biochemical investigations (liver functions, kidney functions, and complete blood count). The

values of parameters remained within normal limits.

This study examined the expression level of CCL27 for distinguishing psoriasis and eczema. CCL27 showed up-regulation in eczema with a mean expression value of (3.32±1.08), compared with psoriasis and control groups (1.72±0.49, 0.37±0.26 respectively). The variation in the expression level was highly significant (P<0.00001). The findings of this study agreed with those of (Quaranta *et al.,* 2014), who noted the significance of CCL27 in skin inflammation; the gene for this substance was discovered to be up-regulated in eczema and down-regulated in psoriasis. Others have also observed that CCL27 mRNA and protein expression was significantly reduced in psoriatic lesions (Riis *et al.,* 2011). The authors suggested NOS2 and CCL27 as disease classification pairs in light of their findings. There was a positive correlation between SCORAD and CCL27 expression level and thus considered CCL27 an important element in the inflammatory process of eczema. While there was a negative correlation between PSAI and CCL27 expression level, and thus considered, CCL27 as an important element distinguishing between psoriasis and eczema. This finding is consistent with previous studies, which demonstrated a strong correlation between disease severity and serum CCL27 concentration, suggesting that evaluating CCL27 is more pertinent to disease severity than detecting other chemokines (Iikuni Noriko *et al.,* 2008; Lu *et al.,* 2016).

Our molecular test's high sensitivity and specificity were based on CCL27, which reflects the intricate disease profile of psoriasis and eczema. CCL27 distinguishes psoriasis from eczema with a specificity and sensitivity for eczema of 100% and 91.2%, respectively, and an AUC of 0.833. CCL27 can be used to differentiate the two disease conditions (psoriasis and eczema) (P<0.018).

5. CONCLUSION

This study clarified the validity of the CCL27 expression in the Egyptian population for differentiating between psoriasis and eczema. This molecular diagnostic tool can be used in pathology labs and routine clinical diagnostics. More studies with sufficient samples of varied racial backgrounds and technical standards are needed to investigate the gene expression patterns and valuable biomarkers for patients with psoriasis and eczema.

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Table 1: Demographic and clinical data among all studied groups

Variables		Control (N=50)	Patients with psoriasis (N=50)	Patients with eczema (N= 50)	P-value
Demographic data					
Age (years)		37.3 ± 15.7	39.6 ± 15.4	31.0 ± 13.8	NS
Gender (F/M)		23/27	30/20	13/37	NS
Smoking status (smoker/non-smoker)		5/45	17/33	6/44	NS
Disease family history (Yes/No)		6/44	24/26	25/25	NS
Disease duration		--	15.5 ± 16.3	106.6 ± 13.8	(P < 0.0001)
Disease scoring	PSAI	--	18.68 ± 9.92	--	(P < 0.0001)
	EASI	--	--	22·8± 9·82	(P < 0.0001)
	SCORAD	--	--	32.9±14.05	(P < 0.0001)
Laboratory parameters					
ALT (IU/L)		18.39±7.42	28.8± 7.2	30.4± 6.9	NS
AST (IU/L)		20.29±8.24	29.3 ± 7.9	32.6± 7.7	NS
Bilirubin (mg/dL)	Total	0.7±0.2	1.25±0.4	1.14±0.5	NS
	Direct	0.1±0.03	0.5±0.02	0.3±0.04	NS
Urea		21.5±7.88	23.3±11.66	21.2±8.88	NS
Creatinine (mg/dL)		0.87±0.18	0.89±0.21	0.84±0.15	NS
CBC	HB	11.6±2.3	11.2±2.6	10.8±3.1	NS
	TLC	6.6±3.9	6.9±3.8	7.1±4.1	NS
	PLT	223±52.9	214±54	205±49	NS

Data were presented as means ± standard deviations; N, number; F, female; M, male; NS, not significant; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HB, hemoglobin; TLC, total leucocyte count; PLT, platelets.

Table 2: The mean expression level of CCL27 in all studied groups

Study groups	CCL27 expression level	P value
Control (n=50)	0.37±0.26	P<0.00001
Patients with psoriasis (n=50)	1.72±0.49	
Patients with eczema (n = 50)	3.32±1.08	

P<0.05 is significant

Table 3: Association between CCL27 expression level and disease severity

Disease severity scoring		CCL27 expression level	P-value
Psoriasis/PSAI	Mild	1.99± 0.47	P<0.001
	Moderate	1.75±0.53	
	Severe	1.43±0.45	
Eczema/ SCORAD	Mild	2.15± 0.9	
	Moderate	3.31±1.13	
	Severe	4.48±1.2	

P<0.05 is significant

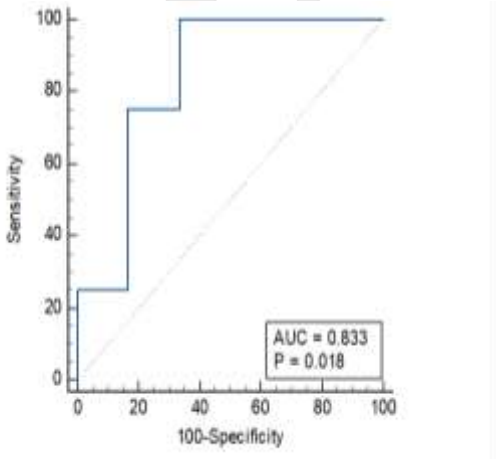

Figure 1: Area under the curve of the receiver operating characteristic (ROC) of the CCL27 to distinguish between psoriasis and eczema