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Role of Maresin-1 in Inflammatory Resolution of Psoriasis (Maresin-1, Novel Therapeutic Alternative in Psoriasis Patients)

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ABSTRACT

Background: Psoriasis is a chronic, recurrent, immune-mediated inflammatory disease that affects 2%–3% of the world's population. It is related to genetic vulnerability, autoimmunity, mental health, and environmental factors. Pathogenesis is highly linked to abnormal interactions between innate immunity, T lymphocytes, and keratinocytes. Maresin 1 (Mar1) is one of the EPA-derived metabolites with substantial anti-inflammatory actions in inflammatory diseases. **Objective:** To investigate the possible association between serum level of Mer1 and psoriasis with variable degrees of severity and compare it with healthy subjects.

Patients and Methods: We conducted a case-control study involving 60 psoriasis patients and 30 apparently healthy individuals of the same age and gender as controls. All participants were recruited from the Outpatient Clinic of the Department of Dermatology and Andrology at Benha University Hospitals. Comprehensive assessments, including history taking, general examination, and skin evaluation, were performed on all participants. Disease severity was determined using the Psoriatic Area and Severity Index (PASI). Serum samples were collected, and Mar1 levels were measured using an ELISA technique.

Results: Mar1 level was considerably lower ($p = 0.007$) in cases compared to controls. At cut-off point of 26.9 pg/ml achieved 96% sensitivity and 93.5% specificity. Mar1 showed a significant negative correlation with disease duration and PASI score. Serum Mar1 significantly predicted the degree of disease severity.

Conclusions: Serum Mar1 significantly decreased in psoriatic patients than controls. It could be valuable for possible diagnostic role and predicting disease pathogenesis, activity and severity of cases with psoriasis.

Keywords: Psoriasis, Disease severity, Maresin-1, ELISA.

INTRODUCTION

Psoriasis is a prevalent, persistent, and inflammatory skin condition characterized by clearly defined, scaly, and reddened patches. It is a widespread global disease, and its occurrence is quite common. In Egypt, the prevalence of psoriasis ranges from 0.19 to 3.0 percent [1]. Psoriasis can manifest at any age, with higher rates observed between 20 and 30 years old and again between 50 and 60 years old. A family history of the illness is often found among those affected [2]. The plaques associated with psoriasis can cause disfigurement, significant discomfort, and may be severe. Itching is typically the most troublesome symptom experienced by individuals with psoriasis [3].

Pathogenesis of psoriasis is marked by aberrant epidermal growth and keratinocyte differentiation. The complex and multifactorial etiology includes genetic, immunologic, and environmental components [4]. In psoriasis, keratinocytes are not only characterized by robust proliferation, but also by altered expression of certain keratins, particularly keratin 16 [5]. Genetic evidence on human leukocyte antigen (HLA) correlations, in addition to data on the existence of oligoclonal T cells in lesional skin and their sensitivity to cutaneous antigens, demonstrate the significance of immune cells in the pathogenesis of psoriasis [6].

Psoriasis has been tied to polymorphisms in the IL23A, STAT3, IL23R, TYK2, and RUNX3 genes. These genes are linked to the Th17 immune response, which plays a role in psoriasis development. Th17 cells may produce several cytokines, such as IL-21, IL-17F, IL-22, tumor necrosis factor (TNF), and granulocyte-macrophage colony-stimulating factor (GM-CSF) [7].

Maresin 1 (Mar1) is an important regulator of the resolution phase in acute inflammation, which is regulated by endogenous specialized pro-resolving mediators (SPMs) [8]. In psoriasis, Mar1 has exhibited anti-inflammatory properties. In an imiquimod-induced animal model of psoriasis, topical Mar1 treatment demonstrated anti-inflammatory benefits. Mar1 accomplished this by suppressing cutaneous IL-17A production by decreasing IL-23 receptor expression [9]. Therefore, topical Mar1 has the potential to be a therapy for inflammatory disorders mediated by IL-17 [10].

This study aimed to investigate the possible association between serum level of Mer1 and psoriasis with variable degrees of severity and compare it with healthy subjects.

PATIENTS AND METHODS

Study Design and Participants:

A case-control study was done on 60 psoriasis patients and 30 seemingly healthy persons of the same age and gender who served as the control group. Cases had a mean age of 34±10.4 years and were composed of 36.7% males and 63.3% females. All patients were recruited from the Outpatient Clinic of the Department of Dermatology and Andrology at Benha University Hospitals between January 2022 and September 2022.

Inclusion criteria: Both sexes of adult patients with psoriasis were included.

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Exclusion criteria: Any chronic disease other than psoriasis, chronic infection, malignancy, Alzheimer's disease, rheumatoid arthritis, or ulcerative colitis, pregnant or lactating females, and those who had taken anti-psoriatic/anti-inflammatory medications in the three months prior to the study.

Methods:

All patients were exposed to a comprehensive history, including onset, course, duration, personal history, medical history, family history, and history of other skin illnesses and medication use, as well as a comprehensive general examination to rule out other systemic disorders. In addition to a comprehensive skin evaluation. At the beginning of the trial, disease severity was determined by calculating the Psoriatic Area and Severity Index (PASI). Serum concentrations of Mar1 were measured in all participants.

Serum level of Mar1 by ELISA technique:

Each participant provided a venous blood sample of two milliliters, which was collected using plain tubes. After allowing the tubes to clot for 20 minutes at room temperature, they were centrifuged at 3000 rpm for 20 minutes. The resulting sera were separated and stored at -80^{o}C until further use. To determine the serum Mar1 levels, a human Mar1 ELISA kit (Shanghai YL Biotech Co., Ltd.) was employed, utilizing a biotin double antibody sandwich technique. The kit has a sensitivity of 0.19 pg/ml and can detect levels ranging from 0.5 pg/ml to 300 pg/ml.

For the ELISA assay, a 40 µl serum specimen was utilized. The Infinite F50 ELISA Reader (TECAN Company, Singapore) was used for measurements, and the Magellan Tracker software (Tecan Trading AG, Männedorf, Switzerland) calculated the readings, with the wavelength adjusted to 450 nm.

Ethical consideration:

This study received ethical approval from the Institutional Review Board, Faculty of Medicine, Benha University. All participants provided written informed consents. The study adhered to the ethical guidelines outlined in the World Medical Association's Declaration of Helsinki for research involving human subjects.

Statistical analysis

The acquired data were revised, coded, tabulated, and analyzed, among other processes. 2017-released SPSS v25.0 (IBM Corp., Armonk, NY) was utilized for the analysis. Mann Whitney Test (U test) was used to assess the statistical significance of the difference of a non-parametric variable between two study groups. Kruskal Wallis was used to assess the statistical significance of the difference of a non-parametric variable between three study groups. Using the Chi-Square test, the association between two qualitative variables was explored. The correlation coefficient was used to determine the magnitude and direction of the linear link between two variables. The ROC curve was utilized to assess the sensitivity and specificity of quantitative diagnostic measures used to categorize patients into one of two categories. With a confidence range of 95 percent, a p-value of less than 0.05 was judged statistically significant.

RESULTS

Mean duration of disease was 13.5 ± 8.2 years. Mean PASI score was 8.7 ± 7.1, 83.3% had early onset, more than half of the cases had progressive course, 33.3% had positive family history and 8.3% had arthritis (Table 1).

Table (1): Features of studied patients

			Cases
Age (years)		**Mean ± SD**	34±10.4
Gender	**Male**	**N (%)**	22 (36.7%)
	Female	**N (%)**	38 (63.3%)
Duration of disease (years)		**Mean ± SD (range)**	13.5 ± 8.2 (1 – 32)
PASI score		**Mean ± SD (range)**	8.7 ± 7.1(0.3 – 26.2)
Severity	**Mild**	**N (%)**	28 (46.7%)
	Moderate	**N (%)**	14 (23.3%)
	Severe	**N (%)**	18 (30%)
Onset of disease (years)	**Early (< 30 years)**	**N (%)**	50 (83.3%)
	Late (50-60 years)	**N (%)**	10 (16.7%)
Course of disease	**Stationary**	**N (%)**	28 (46.7%)
	Progressive	**N (%)**	32 (53.3%)
Family history of psoriasis	**Positive**	**N (%)**	20 (33.3%)
	Negative	**N (%)**	40 (66.7%)
Arthritis	**Positive**	**N (%)**	5 (8.3%)
	Negative	**N (%)**	55 (91.7%)

PASI: Psoriatic Area and Severity Index

Mar1 level was significantly lower in patients (mean 19.85±9.3) compared to control subjects (mean 42.84±12.5) (Figure 1).

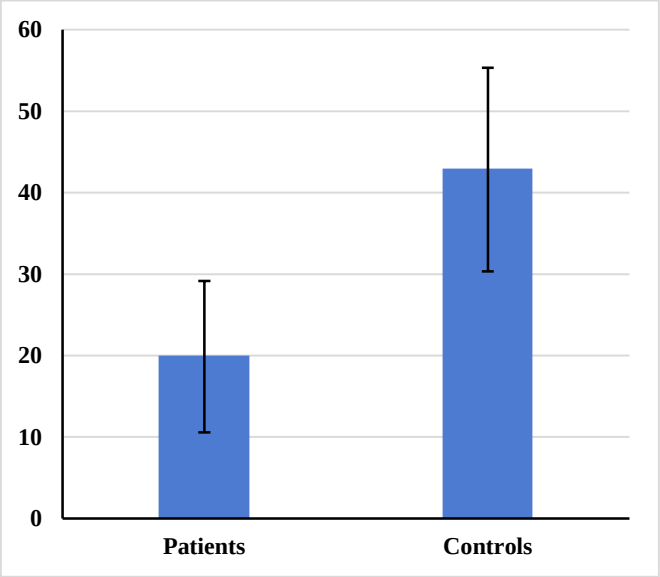

Figure (1): Comparison of serum maresin1 level (pg/ml) between 2 studied groups.

Area under the ROC curve was 96.6%. A cut-off points of 26.9 pg/ml achieved 96% sensitivity and 93.5% specificity (Figure 2).

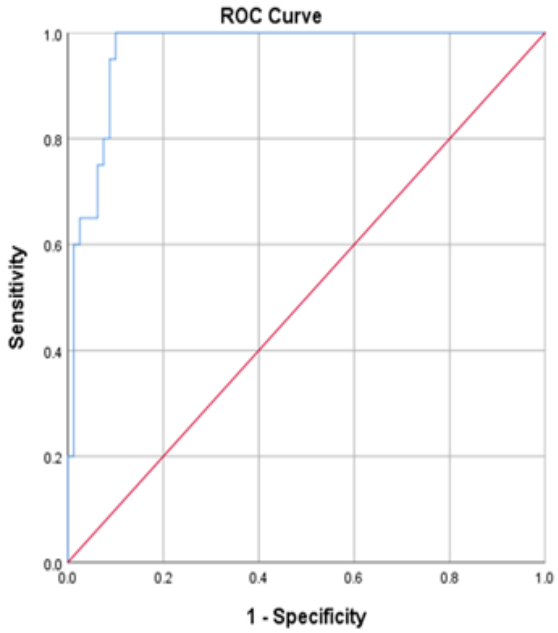

Figure (2): ROC curve analysis of serum maresin1 level (pg/ml)

The serum Mar1 level revealed significant negative correlation with duration of disease as well as with PASI scores (Table 2).

Table (2): Correlation of serum maresin 1 level with age, disease duration and PASI score

	Serum Maresin 1	
	coefficient	P value
Age	-0.161	0.154
Duration of disease	-0.347	0.002
PASI score	-0.758	0.001

PASI: Psoriatic Area and Severity Index

The present results revealed significantly higher serum Mar1 in female patients compared to male patients. No significant difference was found regarding marital status, onset or course of disease, family history or presence of psoriatic arthritis (Table 3).

Table (3): Comparison of serum maresin 1 regarding different demographic and clinical data

		Serum Maresin 1 (pg/ml)	
		Mean ± SD	**P value**
Gender	**Male (n=22)**	16.1 ± 8.2	**0.009**
	Female (n=38)	22.6 ± 9.2	
Marital status	**Married (n=42)**	19.7±9.6	0.878
	Single (n=18)	20.1±8.8	
Onset of disease (years)	**Early (n=50)**	19.9±8.6	0.998
	Late (n=10)	19.8±13.1	
Course of disease	**Stationary (n=27)**	21.9±10.1	0.164
	Progressive (n=32)	17.9±8.3	
	Regressive (n=1)	21.5	
Family history of psoriasis	**Positive (n=20)**	20.5±10.6	0.608
	Negative (n=40)	19.4±8.5	
Arthritis	**Positive (n=5)**	13.5±8.7	0.081
	Negative (n=55)	20.4±9.2	

There was a significant correlation between serum Mar1 levels and the severity of the disease. Analysis of the data revealed that mild cases (mean ± SD: 26.5 ± 2.3 pg/ml) exhibited significantly higher levels of serum Mar1 compared to moderate cases (mean ± SD: 13.8 ± 1.5 pg/ml). Similarly, moderate cases (mean ± SD: 13.8 ± 1.5 pg/ml) demonstrated significantly higher levels of serum Mar1 compared to severe cases (mean ± SD: 8.7 ± 1.2 pg/ml) (Figure 3) (Figure 3).

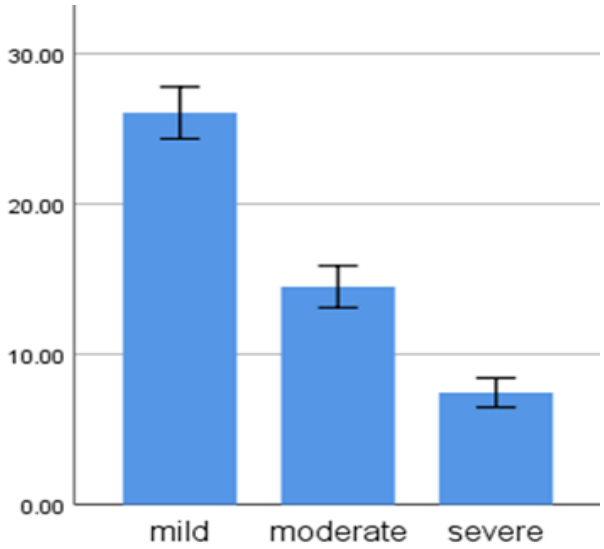

Figure (3): Maresin1 level (pg/ml) in patients according to severity.

DISCUSSION

Psoriasis is a cutaneous chronic inflammatory disease. Several factors participate in the pathogenesis of psoriasis, of which lipid-derived metabolites constitute a pivotal role [11]. Mar1 is one of these EPA-derived metabolites that exhibits many potent anti-inflammatory effects in inflammatory disorders [12].

In the present study, it was found that psoriasis patients had markedly lower concentrations of serum Mar1 compared to healthy controls. Furthermore, among psoriasis patients, males exhibited significantly lower levels of Mar1 compared to females. The relationship between serum Mar1 concentrations and gender has been explored in various medical conditions. **Fang *et al.*** examined the association between serum Mar1 levels and non-alcoholic fatty liver disease (NAFLD). Their study revealed that male NAFLD patients had significantly lower levels of serum Mar1 compared to female NAFLD patients [13], which aligns with our findings. On the other hand, **Miao *et al.*** investigated Mar1 levels in individuals with type 2 diabetes and did not find any significant gender difference [14].

In the present study, the sensitivity of serum Mar1 in distinguishing psoriasis patients was found to be 96%, with a specificity of 93%. Additionally, lower levels of Mar1 in the blood were associated with more severe disease, as indicated by higher PASI scores. These findings suggest that Mar1 may have an anti-inflammatory role in individuals with psoriasis, as the levels of Mar1 in the serum decreased with the duration and severity of the disease. To the best of our knowledge, this is the first study to evaluate serum Mar1 levels in Egyptian psoriasis patients.

In a study conducted by **Saito-Sasaki *et al.*** [9], the anti-inflammatory effects of topical Mar1 were investigated using a mouse model of psoriasis-like inflammation. They examined the levels of Mar1 in the blood and tissues of psoriasis mice. Previous research on specialized pro-resolving mediators (SPMs), including resolvins, protectins, and Mar1, in psoriasis patients revealed significant increases in SPM levels in psoriatic skin lesions compared to non-lesional psoriatic skin and skin from healthy individuals. However, Mar1 levels were undetectable in both the patient and control groups [15].

Another study utilized an animal model of inflammation induced by imiquimod (IMQ), which resembles psoriasis, to examine the anti-inflammatory effects of topical Mar1. By using real-time polymerase chain reaction (RT-PCR) and flow cytometry, the researchers determined that Mar1 did not inhibit IL-23 but did limit the synthesis of IL-17A in skin cells. These inhibitory effects were also observed in a psoriasis model where IL-23 was administered subcutaneously. Moreover, Mar1 suppressed the production of the interleukin-23 receptor (IL-23R) in affected rats, leading to a reduction in skin inflammation [9].

Mar1 effectively impedes the production of IL-17A by CD4+ cells in the skin by reducing the expression of IL-23 receptor (IL-23R) in those cells. The IL-23/IL-17 axis plays a crucial role in the development of psoriasis, as IL-23 triggers the activation of IL-17-producing cells, leading to the aggravation of epidermal hyperplasia and skin inflammation. In mice treated with Mar1, the expression of IL-17A mRNA was inhibited compared to mice treated with a control substance. Moreover, Mar1 exhibits anti-inflammatory properties by suppressing neutrophil migration and cytokine production through the activation of CD8+ T cells [16].

Mar1 demonstrates a wide range of inhibitory effects and induces specific cellular responses. It has been observed to impede the activity of transcription factors T-bet and Rorc, effectively preventing the differentiation of Th1 and Th17 cells. Additionally, Mar1 enhances the phagocytic activity of M2 macrophages, contributing to their immune functions [17]. Through the activation of the G-protein coupled receptor GPR32, Mar1 promotes the generation of Foxp3+ regulatory T (Treg) cells, which play a regulatory role in immune responses [18]. Furthermore, Mar1 effectively suppresses the production of IL-6, IL-1, and TNF-α, which are pro-inflammatory cytokines [19, 20]. In terms of its impact on neutrophils, Mar1 inhibits their infiltration and reduces the production of CXCL-1, a chemokine crucial for neutrophil recruitment. Moreover, Mar1 supports neutrophil apoptosis, facilitating the resolution of inflammatory reactions [21]. Additionally, Mar1 enhances the expression of ICAM-1, which aids in the clearance of neutrophils from tissues [22].

CONCLUSION

Serum Mar1 could be a novel anti-inflammatory hope for patients with psoriasis. It is negative regulator of inflammatory process especially in severe psoriasis with longer duration.

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