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ORIGINAL ARTICLE

Chemerin and calprotectin levels correlate with disease activity and inflammation markers in psoriasis vulgaris

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ABSTRACT

Background: Psoriasis is a chronic inflammatory dermatosis that affects about 2–3% of the general population. We aimed to investigate the relationship between serum chemerin and calprotectin levels and the inflammatory markers that can lead to oxidative damage.

Methods: Fifty patients with psoriasis and 30 healthy controls were included in the study. Levels of chemerin and calprotectin were measured in addition to levels of C-reactive protein, the erythrocyte sedimentation rate, and the white blood cell count to evaluate inflammation.

Results: According to our findings, chemerin and calprotectin levels in the patient group were significantly higher than in the control group ($p < 0.01$ and $p < 0.001$, respectively). Patients with psoriasis were divided into three groups based on the Psoriasis Area and Severity Index: mild, moderate, and severe. The chemerin levels in the severe and moderate groups were significantly higher than in the mild group ($p < 0.01$ and $p < 0.05$, respectively). The calprotectin levels in the severe psoriasis group were also significantly higher than in the mild group ($p < 0.05$). Similarly, the erythrocyte sedimentation rate and levels of fibrinogen and C-reactive protein were significantly higher in patients with psoriasis than in the control group ($p < 0.05$, $p < 0.01$, and $p < 0.001$, respectively). Stepwise regression analysis was used to assess the individual contributing factors. Among these contributing factors, the chemerin levels were observed to be positively correlated with both the Psoriasis Area and Severity Index ($R^2 = 0.111$) and the calprotectin level ($R^2 = 0.445$). Calprotectin was observed to be positively correlated with both the C-reactive protein ($R^2 = 0.119$) and chemerin levels ($R^2 = 0.315$).

Conclusion: The chemerin and calprotectin levels in patients with psoriasis showed that there is an inflammatory process in psoriasis and that these markers are useful indicators of the severity of psoriasis.

Introduction

Psoriasis is a common chronic inflammatory disease with different clinical presentations. The prevalence of psoriasis is about 2–3% in the general population.[1,2] Its etiology is not yet well understood. Although it is known as a T lymphocyte mediated disease, various inflammatory cell types, including dendritic cells, macrophages, neutrophils, and keratinocytes, contribute to the pathogenesis of psoriasis. The histopathology of psoriasis is characterized by distinct inflammatory changes in the dermis and epidermis.[3,4] A cell filtration predominantly composed of neutrophils has been found in active psoriasis lesions. Neutrophil degranulation in particular increases tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6) secretion.[4]

Chemerin is a chemokine that modulates chemotaxis and macrophage and dendritic cell (DC) activation (particularly plasmacytiod DCs and monocyte-derived DCs).[5] It was first observed as a chemotactic peptide involved in both the adaptive and innate immune systems, routing macrophages and DCs that express

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ChemR23 towards inflammatory sites.[5,6] Chemerin is also involved in inflammation by stimulating macrophage adhesion to extracellular matrix proteins and adhesion molecules.[7]

Calprotectin was first identified as an antimicrobial protein localized in the cytoplasm of neutrophil granulocytes.[8] It was also found in neutrophils, monocytes, macrophages, and endothelial and epithelial cells.[9] It was later suggested that this protein might be a promising marker of inflammation.[10,11] S100A8 and S100A9 proteins are secreted by neutrophils and activated monocytes/macrophages and act as chemotactic molecules for these cells.[12–14] Human S100A8 and S100A9 proteins can be found as homodimers, heterodimers, or tetramers $(S100A8/S100A9)_2$. However, the homodimer and heterodimer forms are usually expressed together.[15] These forms are expressed at minimal levels in the normal epidermis. S100A8 and S100A8/A9 (calprotectin) have a positive effect on the growth stimulation of normal human keratinocytes *in vitro*.[16] We aimed to determine chemerin and calprotectin levels in patients with psoriasis and to correlate these parameters with routine inflammatory markers and disease activity.

Materials and methods

Patients

Our study was conducted in 50 patients with psoriasis and a control group of 30 healthy participants. The study was conducted in a dermatology outpatient clinic. Patients were diagnosed with psoriasis after clinical and histological evaluation. Using the Psoriasis Area and Severity Index (PASI), the disease was categorized into three groups as mild (PASI < 5), moderate (PASI 5–10), or severe (PASI > 10).[17]

The exclusion criteria were: any apparent sign of acute or chronic inflammation (e.g., hepatitis, arthritis, or autoimmune disease); previous exposure to biological agents; excessive alcohol consumption (maximum 2 units/day for women, 3 units/day for men); the presence of psoriatic arthritis, acute or chronic infections, or liver or renal impairment; pregnancy or breastfeeding; history of cancer within the previous 5 years; and major trauma. Patients receiving any topical treatment within 1 month, systemic drug treatment, or local or full body phototherapy or photochemotherapy within 3 months were excluded from this study.

The control group consisted of 30 healthy non-smoking volunteers who did not have any systemic or dermatological disease. The study protocol was approved by the local ethics committee. Written informed consent was obtained from all patients and controls.

Laboratory analyses

All participants were tested for white blood cell count (WBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and fibrinogen levels. Fasting blood samples were centrifuged at 3000*g* for 10 minutes at 4°C and serum was extracted. The serum samples were stored at −80°C until testing.

Serum CRP levels were evaluated by immunoturbidimetry (Cobas 501; Roche Diagnostics, Basel, Switzerland). The ESR was determined according to the Westergren method (cutoff 20 mm/h). The WBC count and differential counts were measured using a Hematology Analyzer (Beckman Coulter). Fibrinogen levels were measured by clot detection using a fibrinogen test kit (DiaMed) in a Compact analyzer (Stago).

Chemerin measurement

Serum chemerin levels were measured with a USCN Life enzyme-linked immunosorbent assay kit. The minimum detection limit was 0.061 ng/mL. The intra- and interassay coefficients of variation were lower than 10% and 12%, respectively.

Calprotectin measurement

Calprotectin levels were measured with an Immun Diagnostik–Bensheim enzyme-linked immunosorbent assay kit. The intra- and interassay coefficients of variation were lower than 4.48% and 7.49%. The limit of detection was 3.2 ng/mL.

Statistical analysis

All data were analyzed using the Statistical Package for the Social Sciences for Windows software (SPSS version 16.0; SPSS Chicago, IL, USA). Data are presented as mean ± standard deviation (SD) or percentage values. The differences between groups were assessed by using unpaired *t* tests for parametric data and the Mann–Whitney U test for nonparametric data. Correlations between variables were evaluated using Spearman's rank correlation coefficient. Subsequently, where individual correlations achieved statistical significance, variables were entered into a linear regression model. Statistical significance was defined as $p < 0.05$.

Results

Tables 1 and 2 give the clinical findings and laboratory results of the patients with psoriasis and the control group. Chemerin and calprotectin levels were significantly higher in the patient group than in the control group ($p < 0.01$ and $p < 0.001$, respectively) (Table 1). The ESR, which is a marker of inflammation, fibrinogen, and CRP levels were significantly higher in the patient group than in the control group ($p < 0.05$, $p < 0.01$, and $p < 0.001$, respectively) (Table 1).

Groups of patients with psoriasis, divided into three categories based on the PASI scores, were also compared. The chemerin levels in the moderate and severe psoriasis groups were significantly higher than in the mild psoriasis group ($p < 0.05$ and $p < 0.01$, respectively) (Table 2). Calprotectin levels were significantly higher in the severe psoriasis group than in the mild psoriasis group ($p < 0.05$) (Table 2). CRP levels, which indicate inflammation, were significantly higher in the severe and moderate psoriasis patient group compared with the mild psoriasis group ($p < 0.05$) (Table 2).

The correlation analyses of the patients with psoriasis ($n = 50$) are shown in Table 3. A positive correlation was found between chemerin and calprotectin, CRP, WBC, and the PASI scores ($p < 0.01$, $p < 0.01$, $p < 0.05$, and $p < 0.01$, respectively). The correlation between calprotectin levels and CRP and the PASI score were also positive in patients with psoriasis ($p < 0.05$).

Table 1 Clinical assessments and laboratory findings in patients with psoriasis and the control group.

Test	Control group ($n = 30$)	Psoriasis group ($n = 50$)
BMI (kg/m^2)	26.5 ± 6.56	25.19 ± 4.6
Age (y)	45.1 ± 15.6	42.8 ± 14.7
Sex (female/male)	16/14	27/23
PASI score	—	11.17 ± 8.48
WBC ($10^3/mm^3$)	6.95 ± 1.58	7.79 ± 2.06
ESR (mm/h)	10.36 ± 9.39	17.44 ± 11.73*
Fibrinogen (mg/dL)	290.2 ± 48.55	357.24 ± 116.57**
CRP (mg/dL)	2.84 ± 1.94	6.23 ± 5.1***
Chemerin (ng/mL)	89.14 ± 26.5	133.76 ± 24.01**
Calprotectin (ng/mL)	295.71 ± 83.20	394.43 ± 152.1***

BMI = body mass index; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; PASI = Psoriasis Area and Severity Index; WBC = white blood cells.
*$p < 0.05$.
**$p < 0.01$.
***$p < 0.001$.

Table 2 Laboratory findings of patients with psoriasis based on Psoriasis Area and Severity Index scores.

Test	Mild ($n = 15$)	Moderate ($n = 17$)	Severe ($n = 18$)
WBC ($10^3/mm^3$)	7.76 ± 1.94	6.97 ± 1.27	7.96 ± 2.38
ESR (mm/hour)	18.2 ± 10.52	18.44 ± 17.55	15.8 ± 6.26
Fibrinogen (mg/dl)	362.7 ± 101.5	302.5 ± 160	394.4 ± 83.8
CRP (mg/dl)	4.38 ± 3.98	6 ± 3.56*[a]	8.63 ± 6.71*[a]
Chemerin (ng/mL)	103.66 ± 19.34	136.82 ± 21.9*[a]	56.11 ± 25.22**[a]
Calprotectin (ng/mL)	349.33 ± 77.4	384.1 ± 84.58	440.56 ± 94.62*[a]

CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; WBC = white blood cells.
*$p < 0.05$.
**$p < 0.01$.
[a] Compared with group with mild psoriasis.

Stepwise regression analysis was used to assess the individual contributing factors. Among these contributing factors, the chemerin levels were observed to be positively correlated with both the PASI score ($R^2 = 0.111$) and calprotectin ($R^2 = 0.445$) (Table 4). Calprotectin levels was observed to be positively correlated with both CRP ($R^2 = 0.119$) and chemerin ($R^2 = 0.315$) (Table 5).

Discussion

Many studies have been carried out to determine the pathogenesis of psoriasis; however, its etiology is not yet clear. Many studies have focused on chronic inflammation in psoriasis. In this study, levels of CRP, fibrinogen, and the ESR, which are markers of inflammation, were found to be significantly higher in the patients with psoriasis than in the control group. This supports the view that psoriasis is an inflammatory skin disease (Table 1).

Chemerin has been shown to play a part in the inflammatory process.[6,18] The accumulation of pDCs in psoriatic skin and chemerin/ChemR23 has been shown to be closely correlated. Prochemerin is produced primarily by dermal fibroblasts, but also by mast and endothelial cells. After this precursor of chemerin has been secreted, it is activated by enzymes produced by mast cells and neutrophils found in early psoriatic lesions.[18]

Zheng et al[19] reported that chemerin was expressed in every layer of normal and arrested epithelium. Chemerin levels were found to be particularly high at the periphery of psoriatic lesions. However, conflicting findings have been reported for the blood levels of chemerin in patients with psoriasis. A group of researchers has established higher levels of serum chemerin in patients with psoriasis than in healthy controls.[6,20,21] In contrast, Xue et al[22] established significantly lower levels of circulating chemerin in patients with psoriasis than in healthy controls. Based on our findings, serum chemerin levels in patients with psoriasis were significantly higher than in the control group ($p < 0.01$) (Table 1). A different, but supporting, finding was that chemerin levels were significantly higher in the patients with moderate and severe psoriasis than in patients with mild psoriasis ($p < 0.05$ and $p < 0.01$, respectively) (Table 2). Chemerin production during skin inflammation may therefore be an important source of circulating chemerin.

It has been shown that ChemR23 receptors are upregulated by proinflammatory cytokines such as TNF-α, IL-1β, and IL-6. Recombinant chemerin has also been reported to enhance the production of many proinflammatory cytokines (TNF-α, IL-1β, IL-6, and IL-8).[24] Correlation analysis performed in this study established a positive correlation between chemerin levels and the inflammatory markers CRP and the WBC count and the PASI score, which indicates disease activity (Table 3). These findings showed that chemerin was increased in the acute response and was correlated with disease activity in psoriasis. Gisondi et al[20] and Lora et al[21] established a positive correlation between serum chemerin levels in patients with psoriasis and levels of CRP. A positive correlation was also reported between chemerin and proinflammatory cytokines, including IL-6, TNF-α, and leptin and there was a positive correlation between chemerin and the WBC count.[25–27] Therefore it was suggested that chemerin produced as an inflammatory response might play an active part in regulating the activity of other inflammatory cells and in cytokine production.

Nishibu et al[28] established that monocytes were the most prominent cellular resource in psoriasis and there is a close correlation between increased cytokine levels and the severity of skin lesions. Psoriatic tissue lesions occur as a result of keratinocyte proliferation and the over expression of the S100 protein family, which regulates cell signals, to accumulate inflammatory cells.[16] Studies measuring the calprotectin levels in patients with psoriasis are considered to be insufficient. Garcia-Rodriguez et al[29] established high levels of plasma calprotectin; however, this result was not statistically significant. Aochi et al[30] and Benoit et al[31] found significantly higher levels of serum calprotectin in patients with psoriasis compared with a control group. In this study, we found that serum calprotectin levels in patients with psoriasis were significantly higher than in the control group ($p < 0.001$) (Table 1). Calprotectin levels in the patients with severe psoriasis were significantly higher than those in the patients with mild psoriasis ($p < 0.05$) (Table 2). In a similar manner, Benoit et al[31] established high levels of calprotectin in patients with psoriasis with high disease activity. Patients with arthritis and inflammation were excluded from our study and the high levels of calprotection were considered to be a remarkable finding.

Table 3 Correlation analysis of patients with psoriasis.

	R	p
Chemerin/PASI	0.695	<0.01
Chemerin/calprotectin	0.501	<0.01
Chemerin/CRP	0.739	<0.01
Chemerin/WBC	0.487	<0.05
Calprotectin/PASI score	0.417	<0.05
Calprotectin/CRP	0.444	<0.05
PASI score/CRP	0.394	<0.05
WBC/fibrinogen	0.442	<0.05
ESR/CRP	0.461	<0.05
ESR/fibrinogen	0.469	<0.05
CRP/fibrinogen	0.495	<0.01

CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; PASI = Psoriasis Area and Severity Index; WBC = white blood cells.

Table 4 Correlation of serum chemerin levels with three significant factors by linear regression analysis.

	Regression coefficient	Standard error	p
Constant	2.271	2.214	0.006
CRP	0.112	0.148	0.093
PASI score	0.111	0.051	0.006
Calprotectin	0.445	0.414	0.020

CRP = C-reactive protein; PASI = Psoriasis Area and Severity Index.

Table 5 Correlations of serum calprotectin levels with three significant factors by linear regression analysis.

	Regression coefficient	Standard error	p
Constant	0.172	2.214	0.005
CRP	0.119	0.148	0.018
PASI score	0.404	0.051	0.215
Chemerin	0.315	0.414	0.020

CRP = C-reactive protein; PASI = Psoriasis Area and Severity Index.

We established a positive correlation between calprotection levels and the inflammation marker CRP and the PASI score, which indicates disease activity (Table 3). These results show that calprotectin levels in patients with psoriasis can be considered as a good indicator of existing inflammatory process and that it is correlated with disease activity. Madland et al[32] established a similar positive correlation between CRP levels, the ESR, and the PASI score. Benoit et al[31] reported a positive correlation between calprotectin levels and the PASI score.

In our linear regression model, a positive correlation was also established between chemerin levels and the PASI score (Table 4). Calprotectin was observed to be positively correlated with the levels of both CRP and chemerin, but was not correlated with the PASI score (Table 5). In particular, the positive correlation between calprotectin and chemerin levels suggests that these two cytokine molecules may exert a concomitant effect on patients with psoriasis. These results show that disease activity has been related to chemerin levels. In psoriatic disease, these biomarkers could be relevant in distinguishing between the different clinical variants of the disease, for the assessment of disease activity and severity, and for predicting the outcome of a therapeutic intervention.[33] Psoriasis is a chronic, relapsing inflammatory skin disease.[34] A number of biomarkers have been investigated for use in the assessment of disease activity, but these have given inconsistent results as a result of the stability of the skin lesion.[35] In this respect, the relation between chemerin levels and disease activity are valuable.

The major limitation of our study was the relatively small number of patients. Another limitation of our study was its cross-sectional design; a prospective study on the long-term effects of chemerin and calprotectin in patients with psoriasis should be carried out.

The fact that calprotectin and chemerin, which are considered to have a role in the inflammatory process, were found at high levels in patients with psoriasis and were positively correlated with acute phase reactants suggests that they might influence the occurrence of psoriasis. The role of chemerin and calprotectin in the prognosis of psoriasis is still under investigation. However, the finding that chemerin and calprotectin were expressed at high levels supports the suggestion that these parameters could be used as indicators of disease activity. These findings should be considered as preliminary; larger prospective studies should be carried out to confirm these results.

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