Dermatology Practical & Conceptual

Correlation of Specific Inflammatory Markers With the Occurrence of Depression in Patients With Psoriasis and Their Use as Biomarkers for the Diagnosis of Depression

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Key words: psoriasis, depression, , inflammation, CRP, ESR

Citation: Mitsiou E, Kyriakou A, Parlapani E, et al. Correlation of Specific Inflammatory Markers With the Occurrence of Depression in Patients With Psoriasis and Their Use as Biomarkers for the Diagnosis Of Depression. *Dermatol Pract Concept.* 2024;14(2):e2024104. DOI: https://doi.org/10.5826/dpc.1402a104

Accepted: December 12, 2023; **Published:** April 2024

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Psoriasis is a systemic disease of the skin and nails associated with a wide range of comorbidities such as depression, psoriatic arthritis and metabolic syndrome.

Objectives: The study aimed to examine a potential association between inflammatory markers (C- reactive protein [CRP] and erythrocyte sedimentation rate [ESR]) and depression in patients with psoriasis.

Methods: A total of 80 individuals were enrolled in the study. Case participants included 28 patients diagnosed with Psoriasis (Beck Depression Inventory-II: :0-13) and 24 patients diagnosed with Psoriasis and Depression (Beck Depression Inventory-II:14-63). Twenty-eight (28) healthy participants comprised the control group.

Psoriasis severity was evaluated by using Psoriasis Area and Severity Index, Physician Global Assessment, Body Surface Area and Dermatology Life Quality Index. Written approval was obtained for its use in this study: Cardiff University (09/2015). Other factors considered in the study were obesity using the Body Mass Index, the levels of stress using the Beck Anxiety Inventory, and the presence of insomnia using the Athens Insomnia Scale. Blood draws and inflammatory markers measurements were performed for all participants.

Results: Both CRP and ESR levels were higher in the case group (ie Psoriasis and Depression and Psoriasis) compared to healthy controls. Furthermore, psoriatic patients with depression showed increased CRP and ESR levels compared to those of psoriatic patients without depression.

Conclusions: The evaluation of both CRP and ESR and their use to detect the presence of depression in patients with psoriasis can be an important tool for their holistic treatment of theirs.

Introduction

According to the World Health Organization, psoriasis is defined as "a chronic, non-communicable, painful, disfiguring and disabling disease for which there is no cure and with great negative impact on patients quality of life (QoL). Psoriasis involves the skin and nails and is associated with a number of comorbidities. [1]".

The etiology of psoriasis is complex and has not yet been fully elucidated. In patients with genetic predisposition, inflammation initiation is triggered by an exogenous or endogenous stimulus, leading to the appearance of psoriatic plaque. Several evidence underline the interaction between host genetics and environmental factors in stimulating T-cell-mediated inflammatory processes against self-antigens in psoriasis [2]. Various other cells including dermal dendritic cells, keratinocytes and neutrophils are involved in the immunopathology of psoriasis. The interplay between these cells creates the development of a self-sustained cycle of inflammation around the IL-23/ IL-17 axis.

Lately, research has been focused on the role of Tissue Resident Memory (TRM) T-cells in the course of lesions formation in psoriasis. TRM T-cells, a subset of T-memory cells, appear to produce the proinflammatory cytokines IL-17, interferon-γ and IL-22. Interestingly, even after the remission of psoriatic lesions following treatment, inflammation remains in the apparently healthy tissue in the form of resident TRM cells, as trace of immunological memory [3].

Depression in psoriasis has a substantial effect on the quality of everyday life and the emotional state of patients with psoriasis [4,5].

The association of psoriasis with sleep deprivation, nervousness, and inability to relax have also been shown to negatively affect concentration and daily performance [6,7].

Psoriasis patients are often stigmatized in their daily lives by their visible lesions, which negatively affects their mental health state, causing anxiety and depression [8-11]. The severity of the depressive symptoms is not proportional to the severity of the disease. Psoriasis can be mild, even a small spot may affect the mental sphere of the person with psoriasis [12]. It seems that the onset of depression is more common in women compared to men and in those younger than 31 years [13].

Overall, depression, which very often accompanies psoriasis, is characterized by depressed mood, anhedonia and loss of interest, social withdrawal, sleep, and appetite disturbances. Many times, patients suffering from psoriasis are possessed by feelings of shame, not feeling comfortable in their interpersonal relationships, and do not want to be touched (sexual dysfunction often coexists). There is a mutual relationship between psoriasis and depression, patients with psoriasis show a higher degree of depression than healthy people, and patients with depression show more psoriasis [14].

Although still relatively unknown, it has been postulated that psoriasis in younger adults may have even greater psychological impact as they are more prone to addictive behaviors, such as alcohol, experience loneliness, stigmatization, and low self-esteem, while, suicidal ideations are also more intense, COVID-19 – related stress as well as the continued economic pressure experienced by humanity in the recent years have triggered the occurrence of psoriasis and have greatly increased the incidence of disease relapses, and depressive illness. [15-17].

The immunological background in the pathophysiology of depression has been illustrated by several studies. Furthermore, it has been shown that there are common pathogenetic mechanisms in psoriasis and depression. These two facts can justify the occurrence of increased pro-inflammatory cytokines such as C- reactive protein (CRP), TNF-a, IL-17, and IL-6 in both diseases [18-26] while the brain barrier has been shown to be affected, as well. Stress may also play a role in the exacerbation of psoriasis, by dysregulation of the hypothalamic– pituitary–adrenal (HPA) axis, sympathetic–adrenal–medullary axis, peripheral nervous system, and immune system [27]. Stress-related increased cortisol levels (due to increased ACTH production) have also been associated with psoriasis exacerbation [28]. An important role in the appearance of depression on Brain skin axis, has been shown [28] with the release of the ACTH hormone and the release of inflammatory factors: IFN-a. IL-2, IL-6, IL1β and TNF-α.

Methods

Participants

All participants were recruited from the Psoriasis Outpatient Clinic of the 2nd Department of Dermatology and Venereology, Aristotle University of Thessaloniki.

The study was approved by the Scientific Committee of Papageorgiou General Hospital after permission from the

Hellenic Data Protection Authority. All the participants were thoroughly informed about the scope of the study and were provided with written informed consent, without receiving any financial benefits.

A total number of 52 patients (ie, case participants) was enrolled in the study of whom 28 were diagnosed with Psoriasis (Beck Depression Inventory-II: :0-13), and 24 were diagnosed with Psoriasis and Depression (Beck Depression Inventory-II:14-63). Twenty-eight (28) controls (ie, healthy participants) were also included in the study. The final diagnosis of depression was made by a psychiatrist. As a result, two of our patients with psoriasis and depression were excluded from the second blood sampling because they needed to receive systemic antidepressant treatment.

Blood samples were taken from all participants for the identification and measurement of CRP and erythrocyte sedimentation rate (ESR), as markers of inflammation.

The following inclusion criteria were applied: (a) The patient suffers from moderate to severe psoriasis (body surface area [BSA] > 10 or Psoriasis Area and Severity Index [PASI] > 10 and Dermatology Life Quality Index [DLQI] > 10). (b) The patient suffers from moderate to severe depression. (c) The patient should not follow systemic treatment for psoriasis or depression at the time of joining the study. (d) If a patient was taking systemic treatment for psoriasis or for depression, the period stopped for the respective treatment should not be shorter than the period calculated according to the formula: t1/2 (half-life time of the drug he was taking x 5, according to drugs SPC (summary of product characteristics) [68]. (e) Initiation after admission to study systemic therapy for psoriasis. (f) Greek as a native language. (g) Healthy at the time/ not fever / not infection.

Specific conditions that were considered as exclusion criteria were: (a) Adults over 65 years of age. (b) Under 18 years of age. (c) Pregnancy/breastfeeding. (d) Mild psoriasis: BSA ≤ 10, PASI ≤ 10 and DLQI ≤ 10 [19]. (e) Diagnosed psoriatic arthritis. (f) Coexistence of another autoimmune disease. (g) Immunosuppression. (h) Malignancy. (i) PUVA. (j) Patients with Erythrodermic Psoriasis. (k) Patients with Pustular psoriasis. (l) Patients with Palmoplantar psoriasis. (m) Patients receiving systemic treatment for psoriasis or depression over a shorter period calculated according to the formula: t1/2 (drug half-life) x 5 according to drugs SPC (summary of product characteristics) [68]. (n) Psychiatric disorders other than depression included substance dependence disorder. (o) Fever or any type of infection. (p) Crohn disease (q) Anemia.

Time Points Selection

a. For healthy controls (i) Day 0: taking informed consent and history of the patient, filling out questionnaires, and blood sampling for the measurement of CRP, ESR.
b. For Patients with Psoriasis and Depression and Patients with Psoriasis: (i) Day 0: taking informed consents and history of the patient, filling out questionnaires, blood sampling for the measurement of CRP and ESR, initiation of systemic treatment for psoriasis (ii) 3 months later since Day 0 and if the same systemic treatment for psoriasis continues: history taking, filling out questionnaires, blood sampling for the measurement of CRP and ESR.

Psoriasis Assessment Tools/Methods

Psoriasis Area Severity Index (PASI)[29,30]

Physician Global Assessment (PGA): PGA score is a physician-reported measure of psoriasis severity, using a 6-point measure. Lower PGA scores indicate a better skin condition [31,32].

Body Surface Area (BSA): The palming method is used for the calculation, considering that one palm of the hand is about 1% of the body surface [33,34].

Dermatology Life Quality Index (DLQI): All questions refer to the last week before the exam. Higher DLQI scores indicate lower quality of life [35].

Beck Depression Inventory-II (BDI-II): a 21-item self-report instrument, measuring different aspects of depression on a 4-point severity scale during the last two weeks [36,37].

Body Mass Index (BMI): It is calculated based on the formula: BMI = weight(kg)/heigh)^2 (m^2) and determines the ideal weight of each person based on height and kilograms . Recent data lead to the conclusion that obesity is not just epidemiologically related as a comorbidity with psoriasis but is a causative risk factor for the onset or worsening of psoriasis. Obesity is therefore related to psoriasis with common inflammatory factors while it is mainly characterized by increased leptin, resistin, and chemerin but also decreased adiponectin (adipocytokines) [38,39].

Athens Insomnia Scale (AIS): The Athens Insomnia Scale is an effective and easy sleep analysis tool. There are studies that report that inflammation markers are affected by sleep quality [40,41,42,7,].

Beck Anxiety Inventory (BAI): It is a self-report assessment for measuring various stress symptoms by patients during the last week since completing the questionnaire (ie, Day 0). If the symptoms persist, the help of a mental health specialist may be needed [43].

Inflammation Markers

CRP

CRP belongs to the acute phase proteins and its levels increase in the serum immediately after the onset of the inflammatory reaction. It is produced exclusively in the liver and exhibits both pro-inflammatory and anti-inflammatory properties and plays a role in the non-specific response

(innate/ adaptive immunity). It belongs to blood tests. The detection of C-reactive protein levels in the blood is easy, no special procedures were required, and cheap. The measurement was carried out with the PETIA method (particle-enhanced turbidimetric immunoassay) [44]. The normal value of CRP levels: is less than 0.3 mg/dL.

ESR

ESR is the rate at which red blood cells settle in the plasma and is expressed in mm per hour.

It is classified in blood tests. No special procedures are required before blood sampling. For blood, the collection is used special closed tubes of vacuum air with sodium citrate (sodium citrate 3.2%), usually black in color. The Westergren method measures the distance in millimeters (mm) that red blood cells in anticoagulated whole blood fall to the bottom of a standard upright, elongated tube (Westergren tube) over the course of one hour because of gravity [45]. The normal value varies between 10 and 15 mm in the first hour (for women 12-20 mm). The ESR test is not specific for any disease but is used in conjunction with other tests to identify increased inflammatory activity.

Statistical Analysis

Baseline differences in ESR and CRP levels among groups were analyzed using regression models and adjusting for BMI values. Multiple comparison tests were applied to determine statistically significant pairwise differences based on Bonferroni adjusted p- values. Repeated measures general linear models were applied to examine the differences between the two-time points and between the two groups of patients regarding CRP and ESR levels. The changes were adjusted for baseline values of BMI, PASI score, BGA score, BSA score, DLQI score, BAI score, AIS score, age, gender, and treatment. Statistical significance was set at 0.05 and the analysis was carried out using STATISTICA v 12.0.

Results

Characteristics of Participants

Their baseline characteristics appear in table 1 and other epidemiological characteristics in Table 1 below.

Other Clinical Characteristics of individuals enrolled in the study appears in Table 2 based on a semi-structured interview and patients' medical records.

The study examines the difference observed in CRP and ESR values among the three groups at baseline, as well as the changes observed within a period of three months in the two groups. (psoriasis, psoriasis and depression). Regarding differences at baseline and ESR, statistically significant differences were observed between groups ($F_{2,76}$= 6.312 P = 0.03), after adjusting for baseline BMI values. Specifically, patients suffering from Psoriasis and Depression showed higher levels of ESR than patients diagnosed with Psoriasis but no depression (P = 0.032). The difference between patients suffering Psoriasis and Depression vs controls was also statistically significant as the adjusted p value for multiple comparisons was found to be 0.022. No differences were observed between patients with Psoriasis and controls (P = 1.000). The distribution of data is displayed by a boxplot-type of diagram in Figure 1.

Regarding CRP measurements at baseline, statistically significant differences were observed between healthy controls and both groups of patients suffering from Psoriasis, with or without depression ($F_{2,76}$= 6.937, P = 0.002). Specifically, higher CRP levels were observed in Psoriasis and Depression group compared to controls (P = 0.001) while the Psoriasis group did not differ from the Psoriasis and Depression group (P = 0.210) or the control group (P = 0129).

Table 1 Baseline Characteristics

		Group					
		Healthy controls		Psoriasis and Depression		Psoriasis	
		Mean	Deviation	Mean	Deviation	Mean	Deviation
Age		46.11	11.10	47.96	11.83	49.39	12.72
Age of onset of psoriasis		.	.	32.21	16.08	32.68	15.21
		Group					
		Healthy controls		Psoriasis and Depression		Psoriasis	
		N	%	N	%	N	%
Gender	Male	8.0	28.6%	14.0	58.3%	25.0	89.3%
	Female	20.0	71.4%	10.0	41.7%	3.0	10.7%
Family history of psoriasis	Yes	.0	0.0%	4.0	16.7%	10.0	35.7%
	No	.0	0.0%	20.0	83.3%	18.0	64.3%

Table 2 Summarizes the clinical characteristics of individuals enrolled in the study

		Group					
		Healthy controls		psoriasis+	depression	Psoriasis	
		N	%	N	%	N	%
Psoriatric Nails	Yes	.0	0.0%	16.0	66.7%	16.0	57.1%
		.0	0.0%	8.0	33.3%	12.0	42.9%
TREATMENT FOR PSORIASIS:							
Treatment	Conventional	.0	0.0%	5.0	23.8%	5.0	19.2%
	Biologics	.0	0.0%	16.0	76.2%	21.0	80.8%
Chemoprophylaxis		.0	0.0%	20.0	83.3%	20.0	71.4%
	Past	.0	0.0%	4.0	16.7%	7.0	25.0%
	Now	.0	0.0%	.0	0.0%	1.0	3.6%
MENTAL HEALTH:							
Family history of depression	Yes	2.0	7.1%	3.0	12.5%	1.0	3.6%
	No	26.0	92.9%	21.0	87.5%	27.0	96.4%
Suicidal ideation	Yes	.0	0.0%	3.0	12.5%	1.0	3.6%
	No	28.0	100.0%	21.0	87.5%	27.0	96.4%
CO-MORBIDITIES:							
Hypertension	Yes	7.0	25.0%	9.0	37.5%	5.0	17.9%
	No	21.0	75.0%	15.0	62.5%	23.0	82.1%
Cardiovascular disease	Yes	.0	0.0%	5.0	20.8%	2.0	7.1%
	No	28.0	100.0%	19.0	79.2%	26.0	92.9%
Diabetes	Yes	4.0	14.3%	3.0	12.5%	4.0	14.3%
	No	24.0	85.7%	21.0	87.5%	24.0	85.7%
Dyslipidemia	Yes	4.0	14.3%	9.0	37.5%	8.0	28.6%
	No	24.0	85.7%	15.0	62.5%	20.0	71.4%
HEALTH HABITS:							
Smoking	Yes	15.0	53.6%	10.0	41.7%	16.0	57.1%
	No	13.0	46.4%	14.0	58.3%	12.0	42.9%
Alcohol Consumption	Yes	10.0	35.7%	8.0	33.3%	19.0	67.9%
	No	18.0	64.3%	16.0	66.7%	9.0	32.1%
Drug Use	Yes	.0	0.0%	.0	0.0%	1.0	3.6%
	No	28.0	100.0%	24.0	100.0%	27.0	96.4%
Sports activity	Yes	8.0	28.6%	7.0	29.2%	4.0	14.3%
	No	20.0	71.4%	17.0	70.8%	24.0	85.7%
SEX LIFE:							
Sexual activity	Yes	24.0	85.7%	15.0	62.5%	23.0	82.1%
	No	4.0	14.3%	9.0	37.5%	5.0	17.9%
Sexual activity / affected by psoriasis	Yes	.0	0.0%	14.0	58.3%	7.0	25.0%
	No	.0	0.0%	10.0	41.7%	21.0	75.0%

The distribution of data is displayed by a boxplot-type of diagram in Figure 2.

Differences in ESR and CRP levels were examined between the two-time points (baseline and three months period) for the two groups of patients (Table 4). No significant changes in ESR or CRP values were observed in either group. Comparing the two disease groups, regarding ESR, the initially observed differences at baseline remain statistically significant after adjusting for BMI, PASI score, BGA score, BSA score, DLQI score, BAI score, AIS score, age, gender, and treatment (P = 0.048). The differences, 3 months later, remain statistically significant (P = 0.025). Regarding CRP,

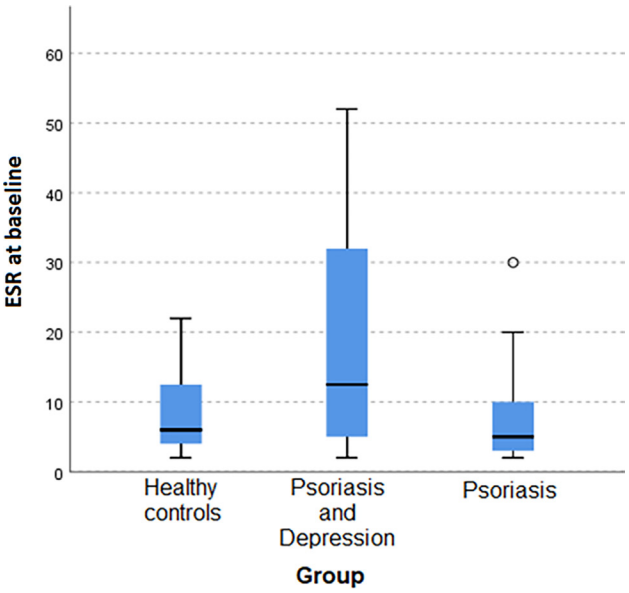

Figure 1. Comparative boxplot of erythrocyte sedimentation rate (ESR) baseline values.

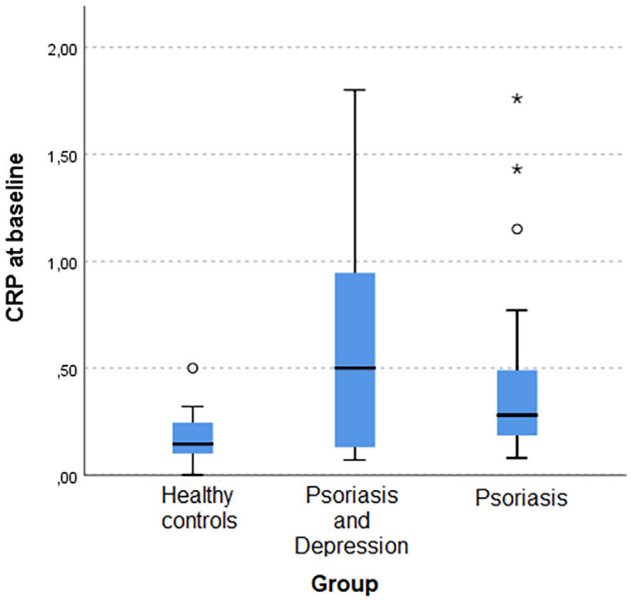

Figure 2. Comparative boxplot of C- reactive protein (CRP) baseline values.

Table 3. Distribution on erythrocyte sedimentation rate and C- reactive protein values in the three groups across the two time points

		ESR at baseline		CRP at baseline	
		Median	Range	Median	Range
Group	• Healthy controls	6.00	20.00	.15	.50
	• Psoriasis and Depression	12.50[a]	50.00	.50[b]	1.73
	• Psoriasis	5.00	28.00	.28 [b]	1.68

[a] Significantly higher ESR levels versus patients with psoriasis
CRP = C- reactive protein; ESR = erythrocyte sedimentation rate.
[b] Significantly higher CRP levels vs healthy controls

Table 4. Distribution on erythrocyte sedimentation rate and C- reactive protein values in the two groups across the two time points

	Group			
	Psoriasis and Depression		Psoriasis	
	Median	Range	Median	Range
ESR at baseline	12.50[a]	50.00	5.00	28.00
ESR at 3m	10.00 [a]	58.00	4.00	28.00
CRP at baseline	.50	1.73	.28	1.68
CRP at 3m	.31	5.47	.21	1.66

[a] Significantly higher erythrocyte sedimentation rate levels versus patients with psoriasis

no differences were observed between the two groups of patients at either time point.

Subgroup analysis indicated significantly higher ESR levels in women at 3 months (median=29, range =56), compared to men (median=4, range = 39), P = 0.005. The Beck Anxiety score was positively correlated to CRP values at baseline (P = 0.027) and at 3 months as well (P = 0.009). Finally, higher CRP values were observed in patients with higher BMI value at baseline (P < 0.001).

Conclusions

The aim of the study was to investigate a potential significant difference in the levels of inflammatory markers CRP and ESR between patients with psoriasis and patients with psoriasis and depression. The potential influence of a three-month systematic treatment for psoriasis on the inflammatory

markers levels was also examined (Conventional systemic therapy, Biologics).

We chose to study these specific indicators of inflammation, because they are easy and economical to measure, while no special preparation for the patient is needed and they are done with a simple blood draw.

Specific inflammatory marker as CRP, is influenced by other factors such as body weight [46], gender (female gender may be associated with increased prevalence of depressive symptoms [48] and levels of anxiety and insomnia [43]. We also know about the immunological background of depression and its relationship with the severity of psoriasis skin lesions [47,49] which affects different aspects of a patient life, including family and sexual life [50], and has an impact on the patient quality of life [50] and can lead, in more serious cases, to increased suicidal ideation [51].

The results of our study confirm the publications so far as we found significantly higher ESR in women with psoriasis and depression and higher CRP was observed in patients with higher BMI at baseline.

Regarding CRP and ESR, measurements were found higher CRP and ESR levels in patients with Psoriasis and Depression and Psoriasis vs healthy controls and higher CRP and ESR levels in patients with Psoriasis and Depression vs patients with Psoriasis. Instead, no significant changes in CRP or ESR values were observed between the two-time points (baseline and three months) after systemic therapy for psoriasis for the two groups of patients (Psoriasis and Depression and Psoriasis). We consider that the 3-month period between the 2 measurements was too short to allow safe conclusions on the possible reduction of CRP and ESR after systemic treatment for psoriasis that patients received.

Therefore, based our results of our study, it would be better to measure them at baseline. Their increased values can alert us not only to the possibility of co-morbidities such as psoriatic arthritis [52] or cardiovascular disease [53] or depression.

If it is also confirmed the existence of depression with the use of special questionnaires, such as Beck, it is an important help for us, as the treating doctors, of choosing the appropriate treatment for our patients suffering from psoriasis. In the literature, there are studies which found an improvement in the depressive symptoms of patients with psoriasis after systematic medication for psoriasis, and after the administration of specific biological factors [54,61] such as etanercept[55,56], adalimumab [57], ustekinumab [58,], while there are also drugs that can worsen it such as apremilast [59]. From Conventional drugs even though cyclosporine has been shown to inhibit Th1 and Th17 pathways exhibiting multifactorial and suppressive anti-psoriatic activity, its antidepressant activity has not been studied [60]. An older drug still used against psoriasis is methotrexate. The antidepressant effect of methotrexate has not been studied. Conversely, depressive symptomatology is reported as an adverse drug effect.

At the end it would be good to inform our patients about their condition and direct them to the appropriate specialist for them (psychiatrist or psychologist or both of them). Regarding pharmacologic treatment, there are studies that evaluated the efficacy of antidepressants, mainly selective serotonin reuptake inhibitors. Nowadays we know the role of the brain-skin axis [28] in psoriasis and depression, which among others leads to decreased serotonin levels. Serotonin is considered the "happiness hormone" because it affects mood and high levels of serotonin are associated with elevated mood and feelings of joy. Low levels of serotonin (serotonergic disbalance) are the key to pathophysiological mechanisms in depression [62]. Brain skin axis [28] by the release of the ACTH hormone, which has receptors among others in the skin, leads to the degranulation of mastocytes and the release of inflammatory factors: IFN-a and the IL-2, IL-6, IL1β, TNF-α by increasing the production of the enzyme Indoleamine 2,3-dioxygenase. This enzyme (Indoleamine 2,3-dioxygenase) catalyzes tryptophan into various other products. Serotonin is produced from tryptophan, resulting in decreased serotonin production due to reduced tryptophan and its products [63]. The relationship between the use of antidepressants for the treatment of depression and the reduction of inflammation and specifically the reduction of CRP has also been studied [64]. However, there is also an opinion that although antidepressants may alleviate psychiatric symptoms, there is evidence that they may be associated with psoriasis symptoms exacerbation [63]. Concerning other therapeutic approaches, a meta-analysis revealed encouraging results with respect to the psychotherapeutic interventions effectiveness on psoriasis outcomes [65]. Cognitive behavioral therapy may be a promising complementary approach for psoriasis patients with depressive symptoms [66]. Still, further research is warranted in this field. Positive psychology interventions strive towards consolidating psychological resources and nourishing positive cognitions and feelings [67] .

In conclusion, psoriasis is a disease requiring a multidimensional therapeutic approach. Our study is based on limited and preliminary data. More studies are needed to help address this important correlation of specific inflammatory markers with the occurrence of depression in patients with psoriasis. The measurement of the values of CRP and ESR and their use to detect the possibility of the presence of depression can be an important tool for the holistic treatment of our patients with psoriasis.

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