

Psoriasis and Associated Psychiatric Disorders

A Systematic Review on Etiopathogenesis and Clinical Correlation

^{a,b}BÁRBARA ISABEL ROQUE CUNHA FERREIRA, MD; ^{b,c}JOSÉ LUÍS PIO DA COSTA ABREU, MD, PHD;
^{a,c}JOSÉ PEDRO GASPAR DOS REIS, MD; ^{a,c}AMÉRICO MANUEL DA COSTA FIGUEIREDO, MD, PHD

^aDepartment of Dermatology, Coimbra Hospital and University Centre, Portugal; ^bCentre for Philosophy of Science, University of Lisbon, Portugal;
^cFaculty of Medicine of the University of Coimbra

ABSTRACT

Introduction and objective: Psoriasis is a chronic skin disease with a high impact on self-esteem and patients' health-related quality of life. In the last decades some studies have pointed out mental disorders associated with psoriasis and the etiopathogenic mechanisms behind that co-existence. This work compiles psychopathology associated with psoriasis and further analyzes the etiopathogenesis of psoriasis and mental disorders. **Methods:** A systematic review of the literature was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and using the "5S" levels of organization of evidence from healthcare research, as previously described. **Results:** Psoriasis is linked with many mental disorders, both in the psychotic and neurotic spectrum. Chronic stress diminishes hypothalamic-pituitary-adrenal axis and upregulates sympathetic-adrenal-medullary responses, stimulating pro-inflammatory cytokines. Then, it maintains and exacerbates psoriasis and some of its mental disorders. High levels of pro-inflammatory cytokines connect psoriasis, psychiatric conditions, and other comorbidities of psoriasis (such as atherosclerosis) within a vicious cycle. Furthermore, the etiopathogenesis of the link between each psychiatric comorbidity and psoriasis has its own subtleties, including the co-occurrence of other comorbidities, the parts of the body affected by psoriasis, treatments, and biological and psychosocial factors. **Conclusion:** The study of psychopathology can amplify our understanding about the etiopathogenesis of psoriasis and associated mental disorders. Patients would benefit from a psychodermatologic approach. The adequate treatment should take into account the mental disorders associated with psoriasis as well as the circumstances under which they occur. (*J Clin Aesthet Dermatol.* 2016;9(6):36–43.)

The skin is the interface between the inner and the outer environment. Thus, it is a ripe field of research of the mind-body connection. The impact of stress factors on the skin is a paradigmatic example: Both physical agents and psychosocial stress factors are linked with the natural history of several skin diseases. In 1946, Wittkower specifically started research on the connection between psychological stress and psoriasis.¹

Psoriasis can be a psychosocial skin disease. Psychosocial stress can maintain and exacerbate it. The etiopathogenesis of the psoriasis-psychological stress relationship includes peripheral nervous system pathways, hypothalamic-pituitary-adrenal axis (HPA), and the sympathetic-adrenal-medullary (SAM) system as well as immune-mediated pathways.¹ However, these mechanisms are still under research.

Patients with psoriasis may have a high prevalence of several mental disorders. A case-controlled study conducted by Kumar et al² reported that 84 percent of

patients with psoriasis had psychiatric comorbidities, a prevalence that was statistically significant ($p < 0.0001$).

Psoriasis has stronger associations with psychiatric disorders than other dermatologic diseases.³ Patients may have specific psychopathologic features that are not commensurate with the extent of skin lesions.³ Studies have shown that these patients suffer from the same deterioration in health-related quality of life as patients with cancer and cardiovascular diseases.^{3,4}

The link between some psychiatric comorbidities and psoriasis has etiopathogenic subtleties that could increase our knowledge about the diseases and their treatments. Studies are needed to explore comorbidities and comprehensively treat these patients.

Thereby, the purpose of this work was to compile and discuss the psychiatric comorbidities associated with psoriasis and the etiopathogenic mechanisms that might explain this connection.

DISCLOSURE: The authors report no relevant conflicts of interest.

ADDRESS CORRESPONDENCE TO: Barbara R. Ferreira, MD; E-mail: barbara.roqueferreira@gmail.com

MATERIALS AND METHODS

The systematic review protocol was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.⁵

Inclusion criteria. The authors selected the articles about psychopathology associated with psoriasis and those which focused the etiopathogenic relationship between psychological stress and psoriasis as well as between psoriasis and each psychiatric comorbidity. They included all study designs with humans published in English, French, German, Portuguese and Spanish between 1990 and February 2015.

Search strategy. The search followed the 5S model of evidence⁶ based on information services described by Haynes. It is a pyramid with five levels of evidence that starts with systems, the top level, and goes down the pyramid to summaries, synopses, syntheses, and studies. The systems level of evidence was not used, as it was not fully developed. The first level used was summaries. At this level, the search was carried out in UpToDate using the words “psoriasis” and “mental disorders” or “psoriasis” and “psychopathology.” At the synopses level of evidence, the search was conducted using the same words in the Evidence Based Medicine database. At the next level of evidence, syntheses, the Cochrane Library was used. At the studies level, the search was in the Medical Subject Headings (MeSH) of PubMed.

The limits applied were the studies with humans published from 1990 to 2015 (February 8) in English, French, German, Portuguese, or Spanish. The authors used the following terms: “Mental Disorders AND Psoriasis” and “Stress, Psychological AND Psoriasis.” They completed the search at the studies level with the words “Psychopathology AND Psoriasis,” but with no date restrictions considering that the search with the limit of 1990 had given no results. A total of 390 articles were retrieved.

Process of study and data collection. The abstracts obtained from the search were reviewed and selected when they focused the inclusion criteria. Repeated studies were excluded. Fifty-seven articles were then selected.

Data collection and analysis. Data extracted from each article that met the inclusion criteria were analyzed following these topics: mental disorders in patients with psoriasis, etiopathogenic mechanisms behind the relationship between psoriasis and psychological stress, and psoriasis and its psychiatric comorbidities.

The terms used follow the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* – DSM-5.⁷

RESULTS

From all the psychiatric comorbidities reported in the literature, the most prevalent seem to be sexual and sleep disorders. More than 50 percent of patients with psoriasis may have sleep complaints.^{8,9} Rieder et al³ highlighted that the prevalence of sexual complaints in patients with psoriasis can reach up to 71.3 percent.

Substance dependence or abuse, somatoform disorders, schizophrenia/other psychoses, bipolar disorder, and eating

TABLE 1. Psychiatric disorders in patients with psoriasis

PSYCHIATRIC DIAGNOSIS		STUDIES: FIRST AUTHOR (YEAR OF PUBLICATION)
Anxiety disorders		Hunter (2013); Thorslund (2013); Mizara (2012); Rieder (2012); Heller (2011); Palijan (2011); Evers (2010); Moynihan (2010); Reich (2010); Janković (2009); Devrimci-Ozguven (2000)
Eating disorders		Crosta (2014); Basavaraj (2011)
Mood disorders	Depressive disorder	Schmitt (2014); Kannan (2013); Shutty (2013); Hrehorów (2012); Kirby (2012); Kurizky (2012); Mizara (2012); Rieder (2012); Basavaraj (2011); Hayes (2011); Kumar (2011); McAleer (2011); Palijan (2011); Poo (2011); Gowda (2010); Kotrulja (2010); Moreno-Giménez (2010); Moynihan (2010); Reich (2010); Freire (2009); Bouguéona (2008); Martín (2008); Hagforsen (2005); Russo (2004); Gupta (2003); Akay (2002); Barankin (2002); Gupta (2002); Devrimci-Ozguven (2000); Sandyk (1990)
	Bipolar disorder	Kaufman (2005); Bouguéona (2008); Demirhan (2012)
Personality disorders/ Personality traits		Crosta (2014); Kotrulja (2010); Gupta (2003); Mazzetti (1994)
Schizophrenia and other psychoses		Yang (2012); Di Nuzzo (2007); Kaufman (2005); Latini (2003); Ascari-Raccagni (2000); Miyaoka (2000); Shimamoto (1990)
Sexual dysfunction		Kurizky (2012); Rieder (2012); Basavaraj (2011)
Sleep disorders		Shutty (2013); Duffin (2009); Gaikwad (2006); Gowda (2006)
Somatoform disorders		Kotrulja (2010); Jankovic (2009); Picardi (2003); Gupta (1990)
Substance dependence or abuse		Adamzik (2013); Rieder (2012); Basavaraj (2011); Dediol (2009); Bouguéon (2008); Meyer (2008); Bahmer (2007); Dellavalle (2005); Naldi (2005); Gupta (2003); Akay (2002); Poikolainen (1990)

TABLE 2. The etiopathogenesis of anxiety disorders in psoriasis

ANXIETY LEADS TO PSORIASIS	PSORIASIS LEADS TO ANXIETY
<ul style="list-style-type: none"> • Stress disturbs epidermal barrier³ • Psoriatic plaques have increased stress-related neuropeptides¹⁸ • Altered sympathetic nervous system (SAM) and dysregulation of both central and peripheral hypothalamus-pituitary-adrenal axes^{13,17,18} • Activated mast cells due to stress-related neuropeptides and upregulated SAM responses^{1,13} • Stress-induced increase in natural killer cells and cutaneous lymphocyte-associated antigen¹ • Increased dendritic epidermal serotonin transporter protein expression¹⁹ 	<ul style="list-style-type: none"> • Chronic itch¹² • Lack of social support: higher risk¹⁰ • Female patients: higher risk¹⁴ • Personality traits/alexithymia^{3,15,16} • Disfigurement¹³ • Stigmatization¹³

disorders are also associated with psoriasis.

Table 1 compiles the selected studies. The authors present the psychiatric comorbidities and the main clinical features and mechanisms behind their link with psoriasis.

Anxiety disorders. Patients with psoriasis have reported more stressful life events in comparison with control subjects.^{1,10,11}

The link between psoriasis and anxiety can be analyzed in two ways (Table 2)—anxiety can lead to psoriasis and psoriasis can lead to anxiety.

Anxiety as a result of having psoriasis. Psoriasis may lead to anxiety because of chronic itch¹² and the disfigurement and stigmatization¹³ caused by having a chronic skin condition. When the patient has a lack of social support,¹⁰ the scores of anxiety are higher because social support is considered a protective factor for psychosomatic diseases, such as psoriasis.¹⁰ A correlation between female gender and higher scores of anxiety in psoriasis was also described.¹⁴

Personality traits, namely alexithymia¹⁵ (difficulty in recognizing emotions in the self), and maladaptive schemas¹⁶ (self-defeating cognitive and emotional patterns built during childhood), are more prevalent in psoriasis and they increase the risk for anxiety disorders. Mizara et al¹⁶ reported two schemas, vulnerability to harm and defectiveness, as predictive of anxiety in psoriasis.

Anxiety may trigger or worsen psoriasis. Stress disturbs the epidermal barrier.³ In psoriasis there is an altered sympathetic nervous system (SAM) activation with increased levels of epinephrine and norepinephrine and decreased levels of cortisol with dysregulation of both central and cutaneous equivalent (peripheral)

hypothalamus-pituitary-adrenal (HPA) axes.^{13,17,18} This dysregulation of HPA axes upregulates pro-inflammatory cytokines and explains the stress-induced exacerbation of psoriasis.^{1,13} Psoriatic plaques have increased stress-related neuropeptides, namely, calcitonin gene-related peptide (CGRP), substance P, and nerve growth factor (NGF). High levels of NGF cause T cell and keratinocyte proliferation as well as mast cell migration and degranulation.¹⁸ Finally, activated mast cells, due to neuropeptides and upregulated SAM responses, have a central role in the cutaneous response to stress and psoriatic plaque evolution.^{1,13}

Stress also increases circulating cutaneous lymphocyte-associated antigen (CLA)+ T cells and CLA+ natural killer (NK) cells. The activation and cutaneous homing of these cells are important in the etiopathogenesis of psoriasis, preceding epidermal changes.¹

Another interesting correlation described was the increase of the expression of serotonin transporter protein (SERT) in psoriatic skin and its link with chronic stress and Psoriasis Area and Severity Index (PASI) scores.¹⁹

Depressive disorders. Depression may result from having a chronic skin condition or it may worsen or trigger psoriasis. Depression and psoriasis can also coexist without an obvious cause-consequence relationship, sharing biological mechanisms (Table 3).

Depression as a result of having psoriasis. Disfigurement and stigmatization connected with psoriasis may lead to depression.^{3,14,20-24} Dissatisfaction with treatments was also positively correlated with depression.^{3,20} Concerning psoriasis treatments, two cases were reported suggesting a link between acitretin and depression but a causal relationship was not proven.^{25,25}

Sexual dysfunction,^{14,26} sleep disorders,^{9,14} and excessive alcohol intake²⁷ are more prevalent in psoriasis and they are linked with depression. They may also contribute to a higher prevalence of depression in psoriasis. Other studies have suggested a correlation between high scores of pruritus or pain and depression, but sometimes it is not clear whether depression is a consequence or an etiologic factor to have pruritus or pain.^{3,11,12,14,22,28,29,30}

Higher PASI scores were also correlated with depression.²⁴ Symptoms of depression are also more common in patients with lesions on the face^{12,24} and genital area.²⁴ A lower self-esteem¹⁴ and some maladaptive schemas,¹⁶ such as social isolation and vulnerability to harm, may predispose those with psoriasis to not deal well with the psychosocial impact of psoriasis, leading to depression.³¹

Personal history of depression increases the risk for a new episode of depression as well.³² Furthermore, a lower sociocultural level as well as being single³² were found to be linked with a higher risk for depression in psoriasis.^{32,33} Female gender also seems to increase the risk for depression, probably due to lower serotonin levels.^{32,33}

The duration of the disease is a controversial factor³⁰: a longer history of psoriasis correlates with lower scores of depression according to Kotrulja et al³⁴ and Moreno-Giménez et al,³² but with higher scores of depression as stated by Schmitt et al²⁰ and Kumar et al.² However, other

TABLE 3. The etiopathogenesis of depression in psoriasis

DEPRESSION EXACERBATES PSORIASIS	PSORIASIS LEADS TO DEPRESSION	PSORIASIS AND DEPRESSION: SHARED ETIOPATHOGENIC MECHANISMS
<ul style="list-style-type: none"> • By increasing the levels of pro-inflammatory cytokines, such as IL-6 and TNF-α³⁶ • By increasing the levels of substance P³⁰ • Depression modulates itch perception and exacerbates pruritus in psoriasis²³ 	<ul style="list-style-type: none"> • Maladaptive schemas^{16,31} • Low sociocultural level; single; female; personal history of depression: higher risk for depression^{32,33} • Sleep disorders^{9,14} • Sexual disorders^{14,26} • Pain and pruritus^{3,11,12,14,22,28,29,30} • Disfigurement and stigmatization^{20,21} • Lesions on face/genital area²⁴ • Higher PASI scores²⁴ 	<ul style="list-style-type: none"> • Abnormal calcium homeostasis³⁹ • High concentrations of substance P^{9,30} • Defect in β-adrenergic function¹⁵ • Low melatonin secretion⁴⁰ • High levels of pro-inflammatory cytokines (IL-1, IL-6, TNF-α)³⁷

authors reported that there was no significant relationship between psoriasis duration and depression.²⁴

Depression may trigger or worsen psoriasis. Poo et al³⁵ showed that depression related to family dysfunction was correlated with exacerbation of psoriasis.

At a biological level, depression can modulate itch perception. Some authors reported that the severity of depression correlates directly with pruritus severity.²³ The role of substance P behind the connection among psoriasis, pruritus, and depression was also highlighted. Depression leads to higher levels of substance P and it promotes proliferation of keratinocytes, skin inflammation, and activation of lymphocytes, worsening psoriasis.³⁰ Depression can also increase the levels of pro-inflammatory cytokines, such as interleukin (IL)-6 and related cytokine networks, exacerbating psoriasis.³⁶

Psoriasis and depression: shared etiopathogenic mechanisms. High levels of pro-inflammatory cytokines such as IL-6 and tumor necrosis factor (TNF)- α are shared by psoriasis and depression, within a vicious cycle. They modify the metabolism of serotonin, norepinephrine, and dopamine in the limbic system and basal ganglia, leading to symptoms of depression.^{3,18,30,37,38} Pro-inflammatory cytokines, such as IL-6, drive maturation of naïve T cells to produce T helper (Th)17 cells, which have a role in psoriatic lesions.¹⁸

Palmoplantar pustulosis is linked with abnormal calcium homeostasis with changes in serum calcium. Abnormal calcium levels may also be linked with symptoms of depression. Thus, further studies are needed to clarify the exact role abnormal calcium levels play in higher prevalence rates of depression in palmoplantar pustulosis.³⁹

A relationship between lower melatonin secretion, depression, and psoriasis vulgaris was also reported.⁴⁰ Other studies found that a defect in β -adrenergic receptor function influenced epidermal cell division, having a role in psoriasis. A role in the etiopathogenesis of depression was also described.¹⁵

Bipolar disorder. As described above, pro-inflammatory cytokines, such as TNF- α , are associated with depression. Antidepressants have been linked with cycling

into manic episodes as a result of the resolution of pro-inflammatory cytokine-induced depression. Thereby, we may suppose that the treatment of a patient with a personal history of bipolar disorder, or depression, with an anticytokine therapy, such as a TNF- α antagonist, could also result in cycling into manic or hypomanic episodes because of the decreased levels of TNF- α . Therefore, in patients with mood disorders, especially bipolar disorder, the use of a TNF- α antagonist should be carefully monitored.⁴¹

Genetics and its impact on cell-mediated immune system can explain the co-occurrence of bipolar disorder and psoriasis. Demirhan et al⁴² found a correlation between immunological changes (high CD4/CD8 ratio) and chromosomal aberrations (aneuploidy of chromosome 8) in a family with bipolar disorder and psoriasis.

On the other hand, psychological stress can trigger both psoriasis and manic episodes. Moreover, patients with bipolar disorder usually have substance abuse, which, in turn, may worsen psoriasis.³⁰

Eating disorders. Basavaraj et al¹¹ stated that overeating was a common destructive “coping” mechanism in patients with psoriasis. Crosta et al⁴³ mentioned that, in psoriasis, overweight and obesity were more associated with an underlying eating disorder than in the general population. They also added that binge eating disorder was a psychopathological factor for the development of metabolic syndrome in psoriasis. Using the “Eating Disorder Inventory” to measure symptoms of eating disorders, they found that body dissatisfaction and interpersonal distrust were statistically significant in psoriasis.⁴³

Personality disorders and traits. Rubino et al⁴⁴ mentioned that, in psoriasis, the most prevalent personality disorders are schizoid, avoidant, dependent, and compulsive. Mazzetti et al⁴⁵ reported that 17.5 percent of patients were moody, 12.5 percent were anxious, and 6.25 percent had a schizophrenic trait.

More recently, early-onset psoriasis has been associated with alexithymia, which is a personality trait that would render the patient more susceptible for stress factors.²³ Kotrulja et al³⁴ highlighted that psoriasis of late-onset (mean

TABLE 4. The etiologic factors for sleep and sexual disorders in psoriasis

SLEEP DISORDERS IN PSORIASIS: ETIOLOGY	SEXUAL DISORDERS IN PSORIASIS: ETIOLOGY
Depression ^{9,37}	Risk factors for cardiovascular disease ³
Obstructive sleep apnea ⁹	Low self-esteem/psychological factors ^{3,26}
Pain of skin lesions ^{9,52}	Other psychiatric comorbidities: depression, ^{11,26} substance dependence, or abuse
Parts of the body affected ⁸	Pruritus ¹¹
Pruritus ^{9,37}	Psoriatic arthritis ¹¹
Psoriatic arthritis/joint pain ⁵²	Side effects of psoriasis treatments ²⁶

age of 52) would have a higher risk for histrionic and obsessive personality traits, the latter increasing the risk for hypochondriasis.

Schizophrenia and other psychoses. Yang et al.⁴⁶ found that patients with schizophrenia were at higher risk for psoriasis. PSORS1 on chromosome 6p is considered a major locus for psoriasis vulnerability. Schizophrenia can be linked with chromosome 6p on a locus close to PSORS1.⁴⁶

Miyaoka et al.⁴⁷ reported two patients with psoriasis vulgaris and schizophrenia with a significant improvement of both conditions after introducing haloperidol for schizophrenia. Miyaoka et al reported another patient with schizophrenia and psoriasis vulgaris treated with another typical anti-psychotic medication (levomepromazine), which also helped his psoriasis.

Shimamoto et al.⁴⁸ described another case of remission of psoriasis with a typical anti-psychotic (chlorpromazine). However, the effect of atypical anti-psychotic drugs on psoriasis seems to be different. Latini et al.⁴⁹ described two patients with psychosis who had worsening of pre-existing psoriasis after the introduction of olanzapine. Ascari-Raccagni et al.⁵⁰ reported another case of a dramatic worsening of psoriasis after starting olanzapine in a patient who also had schizophrenia.

Some treatments used for psoriasis can also change the course of the associated psychotic diseases. Kaufman et al.⁴¹ described a patient who developed a manic episode with psychotic symptoms shortly after introducing an anti-TNF drug (etanercept) to treat psoriasis, pointing out the role of TNF in both diseases. Di Nuzzo et al.⁵¹ reported another interesting case: a patient with plaque psoriasis and paranoid schizophrenia. Cyclosporine exacerbated psychotic symptoms within a few weeks after its

introduction. Those symptoms disappeared after stopping cyclosporine. The role of IL-2 in both conditions was highlighted.

Sexual disorders. The etiology of sexual disorders in psoriasis is listed in Table 4. A decreased sexual desire as well as orgasmic disorder and erectile dysfunction are all prevalent. Psoriasis decreases self-esteem and this can explain some of these cases.^{3,26}

Higher scores of psoriatic arthritis, psoriasis severity, and pruritus correlate with sexual disorders in these patients.¹¹ Since depression is prevalent in psoriasis, it may also explain higher scores of sexual dysfunction in psoriasis.^{11,26} Other authors mentioned that patients treated with methotrexate would have a higher risk for erectile dysfunction and loss of libido.²⁶ Some studies also reported that female gender would be a risk for sexual disorders in the context of psoriasis.^{3,11}

Finally, the link between psoriasis and risk factors for cardiovascular disease may also explain the etiopathogeny of erectile dysfunction in patients with psoriasis and justify why the prevalence is higher than in the general population.³

Sleep disorders. The etiology of sleep disorders is listed in Table 4. In psoriasis, sleep disorders may include initial insomnia, an increase of nocturnal awakenings, early morning awakenings, and daytime sleepiness.³⁷ These sleep disorders may be secondary to depression.^{9,37}

According to other authors, the following specific clinical features of psoriasis may predict and increase the risk for sleep disorders: psoriatic arthritis,⁵² pruritus,^{9,37,52} and pain due to the psoriasis plaques^{37,52}; lesions on palms, soles, or scalp⁸; and the impact of this chronic skin condition on self-esteem.⁵² Duffin et al.⁵² reported that psoriatic arthritis can be considered the most significant predictor.

Obstructive sleep apnea (OSA) occurs in a statistically significant percentage of patients with psoriasis.³⁷ Elevated levels of TNF and IL-6 are shared by psoriasis and OSA.³⁷

Finally, the link between pruritus and sleep disorders involves substance P. The levels of substance P are altered by stress both in central nervous system and in psoriatic lesions. This causes poor sleep quality and may lead to low mood.³⁷

Somatiform disorders. Patients with psoriasis exhibit higher scores of hypochondriasis, hysteria, and somatization. As previously exposed hypochondriasis and hysteria may be connected with specific personality traits of patients with psoriasis of late-onset.³⁴

Psychosomatic factors, namely stressful life events, lack of social support, and attachment insecurity, may explain why patients with psoriasis have greater scores of somatization.^{10,53} Moreover, the presence of depression in psoriasis may modulate itch perception and then exacerbate symptoms of pruritus.⁵⁴

Substance abuse and dependence. Destructive “coping” mechanisms, including drinking alcohol and smoking, are common in patients with psoriasis.^{11,55} Substance abuse results from a psychiatric comorbidity of psoriasis, such as depression,³⁰ or from the strong

psychological impact of having a stigmatizing skin disease.¹¹ Alcohol intake may act as a source of positive affect.⁵⁶

Some authors reported that smoking more than 20 cigarettes/day increases the risk for psoriasis when the patient is a female or when there is a first-degree relative with psoriasis.⁵⁷ Another study found that smoking more than 10 cigarettes/day²³ would be enough to increase the severity of psoriasis.

Dellavalle et al⁵⁸ reported that ex-smokers had a higher risk for psoriasis than those who currently smoke because of the blockade of the immunosuppressive effect provided by smoking. Another study described that passive smokers would have a higher risk for psoriasis too.³

In smokers, the cutaneous features of psoriasis were described as more acral⁵⁷ and pustular.⁵⁹ No specific patterns of cutaneous lesions were described for those with alcohol abuse. The risk of developing psoriasis would increase when the alcohol consumption was higher than 50 g/d.⁵⁷

Smoking alters immune responses through T-cell and inflammatory cytokines activation, including TNF- α .³ Chronic alcohol consumption and nicotine abuse increase TNF levels.⁶⁰

Ethanol increases the activity of transcription factors for keratinocyte growth factor receptor, cyclin D1, and $\alpha 5$ integrin, leading to keratinocytes hyperproliferation.⁶¹ Alcohol also diminishes the immune response, increasing the vulnerability to have infections that can trigger psoriasis.^{3,61}

Genetics also contributes to the etiopathogenesis of psoriasis and substance dependence or abuse. In smokers, some variants of CYP1A1 were considered protectors against psoriasis.³ In alcohol drinkers, those with genotype HLA-DQA1* 0201 had a higher risk of developing psoriasis.⁶¹

DISCUSSION AND CONCLUSION

Many mental disorders are associated with psoriasis and the etiopathogenesis of that connection is wide. Some psychiatric comorbidities may result from the psychosocial impact of having a chronic skin condition.¹³ Anxiety, depression, sexual disorders, and substance abuse are some examples.

On the other hand, psoriasis can be maintained and exacerbated by an underlying psychiatric condition within a vicious cycle. This means that the psychiatric condition, such as anxiety symptoms or even a specific anxiety disorder, worsens the skin disease. The aesthetic consequences of having psoriasis are worsened as a consequence, worsening the associated anxiety condition.

As described by Moynihan et al,¹⁸ there is a biological interconnection among depression, anxiety, and psoriasis. Psychological stress factors are processed in paraventricular nucleus of hypothalamus, to produce corticotropin releasing hormone (CRH), resulting, afterwards, in the secretion of corticotropin (ACTH) and cortisol. At the same time, the locus coeruleus mediates the activation of the sympathetic system causing the release of norepinephrine. Corticosteroid receptors may become

insensitive to the continued effects of cortisol and the effect of catecholamines on macrophages becomes preponderant. Then, the secretion of TNF- α , IL-1, and IL-6 is stimulated. Psoriatic plaques also contribute to the production of these pro-inflammatory cytokines. The effect of those cytokines on the brain induces or exacerbates symptoms of depression and re-activates the HPA axes (central and peripheral) and the sympathetic system in a vicious cycle.^{13,17,18}

As well as those biological mechanisms, specific psychopathological features, such as alexithymia¹⁵ or maladaptive schemas,¹⁶ can increase the risk for depression or anxiety in psoriasis. The side effects of treatments used for psoriasis may explain some of its associated mental disorders as well.^{26,51}

Several studies pointed out that female gender contributes to a higher risk for secondary psychiatric comorbidities in the context of having psoriasis.^{3,11,14,32,33} The areas of the body where the lesions are more expressive, such as when the visible areas are affected, may be another important fact that could increase the risk for mental disorders.^{12,24}

Therefore, the etiopathogenesis of mental disorders associated with psoriasis includes a broad range of factors and mechanisms. Some of them are specific in each associated disease while others are shared by many of them. Thereby, patients with psoriasis would benefit from psychodermatologic assessment in order to define whether or not an underlying mental disorder exists, the kind of psychopathology and the underlying etiological factors. This would improve the patient treatment approach. For instance, some treatments for psoriasis, such as TNF antagonists, may lead to manic or hypomanic episodes. So, potential side effects should be thoroughly analyzed when the patient has a personal or family history of bipolar disorder.

High levels of pro-inflammatory cytokines may connect psoriasis and not only the associated psychiatric disorders, but also other comorbidities. For example, high levels of pro-inflammatory cytokines are also shared by atherosclerosis and metabolic syndrome and they lead to endothelial dysfunction, having a central role in the etiopathogenesis of cardiovascular disease and erectile dysfunction.⁶² Therefore, psoriasis comorbidities may influence each other and we might suppose that, when we treat one of them, the others may have biological changes with or without a significant clinical change.

Another interesting topic would be the biochemical mechanisms that explained the improvement of cases of psoriasis with typical anti-psychotic drugs. This should be clarified.⁴⁷ It would be interesting to explore the biochemical mechanisms behind the dermatologic adverse effects of olanzapine as well.^{49,50} Another important matter to develop would be the benefit of selective serotonin reuptake inhibitors (SSRI) to treat psoriasis, considering that SSRI downregulates T cell proliferation.¹⁹ Perhaps further studies on these topics could improve the understanding of psoriasis with therapeutic relevance.

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