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The Psoriasis-Depression Nexus: A Critical Review of Clinical and Biological Underpinnings

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ABSTRACT

Psoriasis is a chronic inflammatory skin condition that can severely diminish a patient's quality of life. Beyond the physical manifestations, psoriasis has been linked to an increased risk of psychological comorbidities like depression. This review aims to synthesize the available evidence examining the relationship between psoriasis and depression.

Methods: A comprehensive literature search across multiple electronic databases (PubMed, PsycINFO, Embase) was conducted to identify relevant studies exploring the association between psoriasis and depressive symptoms or disorders. Both observational studies and intervention trials were included**.**

Results: Numerous cross-sectional and longitudinal studies consistently report a higher prevalence of depression among individuals with psoriasis compared to the general population. The risk and severity of depressive symptoms appear positively correlated with the extent of psoriasis lesions and degree of psychosocial impairment. Potential underlying mechanisms discussed include psychosocial factors (stigma, low self-esteem), biological factors (inflammatory processes, cytokine dysregulation), and shared genetic predisposition. However, the causal direction remains unclear. Limited intervention data suggests effective psoriasis treatment may help alleviate coexisting depressive symptoms.

Conclusion: This review highlights the substantial psychological burden associated with psoriasis, underscoring the importance of routine screening and appropriate management of depressive disorders in this patient population. An integrated multidisciplinary approach combining dermatological treatment with psychological interventions may enhance overall well-being and quality of life.

Keywords: Psoriasis, Depression, Risk factors, Inflammation

INTRODUCTION

Psoriasis is a chronic inflammatory condition that primarily impacts the skin and joints. The clinical features include red, scaly patches on the skin and a relapsing-remitting course. On microscopic examination, psoriasis is characterized by excessive proliferation of epidermal cells, dilated and prominent blood vessels, and a dense accumulation of lymphocytes around the vessels. Current understanding recognizes psoriasis as an autoimmune disorder. [1]

Estimates suggest that psoriasis affects around 1-3% of the global population. [2] While predominantly involving the skin, psoriasis also frequently impacts the joints. Approximately 3% of psoriasis patients develop psoriatic arthritis annually, with some studies reporting up to 42% of psoriasis patients having concomitant psoriatic arthritis.[3-4] Furthermore, individuals with psoriasis demonstrate an elevated risk for metabolic comorbidities like obesity, diabetes, and cardiovascular events. [5-6]

The increased risk of depression in psoriasis patients can be attributed to multiple factors, encompassing both biological mechanisms and psychosocial impacts. The inflammatory cytokines involved in the pathogenesis of psoriasis have been implicated in the development of depression. For instance, administering interferon as a treatment for hepatitis C can trigger or exacerbate psoriasis while also commonly causing depression as a side effect. [7-8] Conversely, reports suggest that certain psoriasis treatments, such as tumor necrosis factor (TNF) inhibitors [9-10] or an interleukin-12 and 23 inhibitor,[11] can improve mood symptoms. Beyond biological factors, the physical appearance and

discomfort associated with psoriatic lesions can profoundly impact self-image and quality of life. [12-13] Patients with visible lesions may attempt to conceal their skin with additional clothing, experience difficulties with sexual intimacy, and avoid physical activities. [12] Feelings of shame, worry, and frustration are commonly reported, which can impair work and leisure pursuits.[14] These biological changes and psychosocial burdens can culminate in clinical diagnoses of depression and other psychiatric disorders, as well as suicidal ideation. Although predicting such outcomes remains challenging, individuals with psoriasis demonstrate an increased prevalence of alexithymia, which is the inability to recognize or describe one's emotions. [15] This emotional disconnect can lead to an underestimation of depression and suicidality, with many studies noting a discrepancy between the severity of skin lesions and the levels of distress experienced. [16-20] The distress caused by psoriasis can, in turn, impair the efficacy of treatments, [21] potentially creating a vicious cycle of suboptimal clinical outcomes exacerbating psychological distress. Therefore, identifying psoriasis patients at high risk for depression and suicidal tendencies is crucial, as addressing these psychiatric comorbidities may not only improve mental health butalso enhance the overall management of psoriasis.

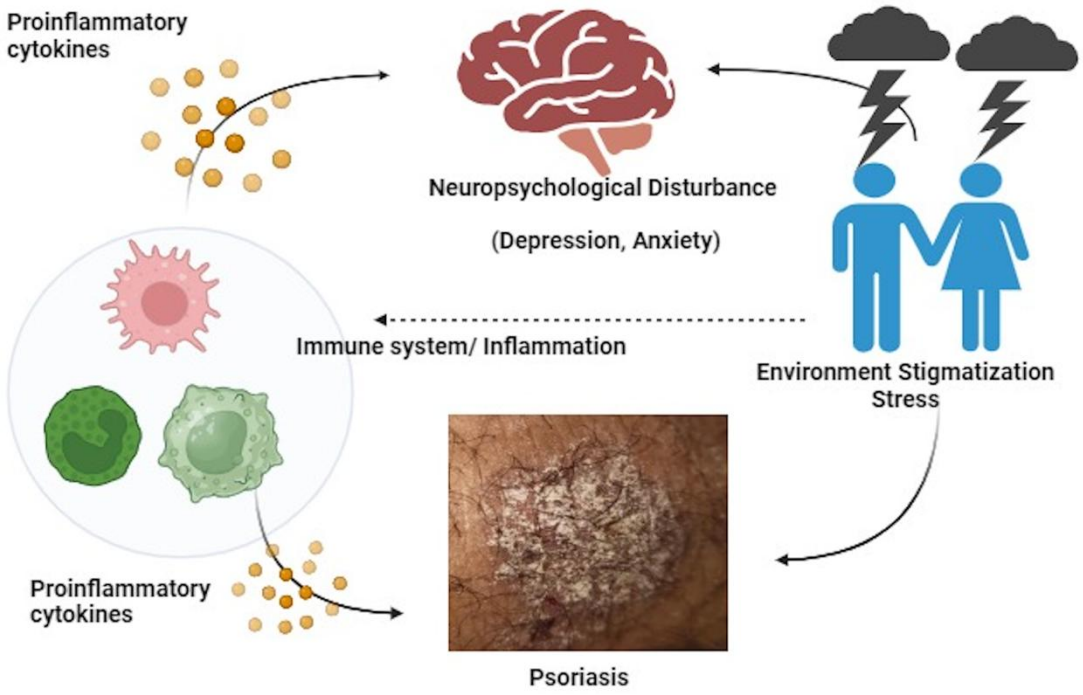

Figure 1: Factors affecting psoriasis

Psychosomatic medicine is a multidisciplinary field that investigates the influence of social, psychological, and behavioral factors on bodily functions, their interrelationships, and overall quality of life.[22] This article focuses on the topic of psychodermatology, which is a subspecialty of psychosomatic medicine that deals specifically with the skin.[23] A psychodermatological disorder is a condition that involves an interplay between the nervous system and the integumentary system (skin). These disorders can be categorized into three main groups: psychophysiological disorders, primary psychiatric disorders with dermatological manifestations, and secondary psychiatric disorders resulting from dermatological conditions.[24]

Risk Factors

Age

Psoriasis exhibits a bimodal pattern in terms of age of onset, with one peak occurring between 15-20 years and another peak around 55-60 years of age.[25] In a cross-sectional descriptive study involving 101 psoriasis patients, those who developed the condition before the age of 20 showed an increased incidence of depression compared to patients whose onset occurred at 20 years or later.[26]Early age of psoriasis onset also appears to be a risk factor for suicidality. A large population-based cohort study compared 766,950 individuals without psoriasis to 149,998 patients with psoriasis. The study found that younger psoriasis patients demonstrated a higher risk for suicidal behaviors, defined as suicidal ideation, attempted suicide, or completed suicide.[27]

Gender

There is conflicting evidence regarding the effects of gender on psoriasis and associated psychiatric conditions. One study in the US evaluated the impact of psoriasis on quality of life using the Psoriasis Disability Index (PDI) in a randomly selected group of psoriasis patients. The PDI consists of 15 questions about daily activities, leisure,

relationships, work, and treatment, as well as a global question about the overall effect on daily life. Higher numerical scores indicate a greater detrimental impact on quality of life. The study found that younger patients experienced the highest disease burden on their quality of life, and female patients reported higher PDI scores than males.[28] However, another study involving 6,497 Nordic patients found no significant gender differences in PDI scores.[29] Notably, male patients in this study had higher Psoriasis Area and Severity Index (PASI) scores, suggesting that despite more severe disease, men may be less likely to report decreased quality of life.[29]

The relationship between gender and suicidality is not well-established. In the general population, evidence suggests that while females are at higher risk for suicide attempts, completed suicides are more common in males.[30-31] This is likely attributable to the use of more lethal methods in males.[32] In patients with psoriasis, two studies found no significant effect of patient gender on suicidal ideation or suicidal behaviours.[27,33] Although suicidality is more prevalent in psoriasis patients compared to the general population, it does not appear to differ between males and females within this patient group.

Severity of Disease

The degree of severity in psoriasis plays a crucial role in the overall well-being of patients affected by the condition. As the severity of psoriasis increases, so does the burden of associated medical comorbidities in this patient population.[34] Individuals with severe forms of psoriasis face an elevated risk of overall mortality, while milder cases do not seem to impact mortality rates.[35] Despite potential disconnects between the extent of visible skin lesions and the levels of psychological distress experienced, the severity of psoriasis may have an influence on the prevalence of depression and suicidal tendencies.

Obesity

Obesity stands out as the most significant risk factor for psoriatic disease. The strongest population-level evidence supporting the crucial role of obesity in psoriatic disease comes from studies conducted in Denmark and Sweden. In the Swedish Obese Subjects study, a cohort of 1,991 individuals who underwent bariatric surgery and 2,018 obese controls, all without psoriasis at baseline, were followed up for up to 26 years.[36] The mean body mass index (BMI) was 40 in the control group and 42 in the surgery group. Among the surgery group, the adjusted hazard ratio (HR) for developing psoriasis was 0.65, indicating a 45% reduction in risk. Smoking and a longer duration of obesity were negatively associated with this risk reduction. In a Danish study, 12,364 individuals without psoriasis underwent gastric bypass surgery and were followed for 10 years.[37] The adjusted HR of developing psoriasis in this group was 0.52, corresponding to a 48% reduction in risk.

Smoking

The Danish National Birth Cohort study, which investigated 25,812 children, found that prenatal smoking increased the risk of psoriasis by 1.47-fold, maternal/paternal smoking during the first year after birth by 1.49-fold, and smoking during childhood by 1.37.[38] For pregnant women who smoked more than 16 cigarettes per day, the risk of their child developing psoriasis was increased by 2.96-fold. A systematic review revealed that the risk of developing psoriasis was 1.84 times higher in ever-smokers compared to non-smokers.[38] However, population-based data on the effect of smoking cessation on psoriasis risk in former smokers is currently lacking.

In addition to activating adaptive immune responses, tobacco smoke-derived benzo(a)pyrene can activate the aryl hydrocarbon receptor (AhR)-inducible pathways. This AhR activation leads to increased expression of interleukin-8 (IL-8) in a CYP1A1-dependent manner.[39] IL-8 is a key chemokine that drives the recruitment of neutrophils into the epidermis, a characteristic feature of psoriatic skin lesions.

Common Fundamentals of Psoriasis and Depression

One possible explanation for the close association between psychological burden and psoriasis is the common societal stigma faced by patients with visible skin manifestations. This hypothesis is supported by findings that perceived social stigmatization is a strong predictor of depressive symptoms in individuals with psoriasis. [40] However, this relatively straightforward explanation may not fully account for all the observed effects.

Another hypothesis, which is gaining increasing attention, suggests that immunological factors could play a role in the association between depressive symptoms and inflammatory skin diseases like psoriasis. For years, depression was attributed to reductions in monoaminergic neurotransmitters in the central nervous system (CNS), as monoamine agonists have been found to improve symptoms in a subset of patients.[41-43] However, it is now well-established that cytokine-mediated communication between the immune system and the brain plays a central role in the pathogenesis of depression.[44-47] Studies have reported elevated serum levels of pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNF-α), interleukins (IL)-1, IL-1β, IL-2, IL-6, IL-8, IL-17, IL-23, and C-reactive protein (CRP), in patients with depression without other inflammatory comorbidities.[48-52] Conversely, a high prevalence of depressive symptoms has been observed in patients with chronic inflammatory conditions, such as rheumatoid arthritis or inflammatory bowel disease.[53-55]

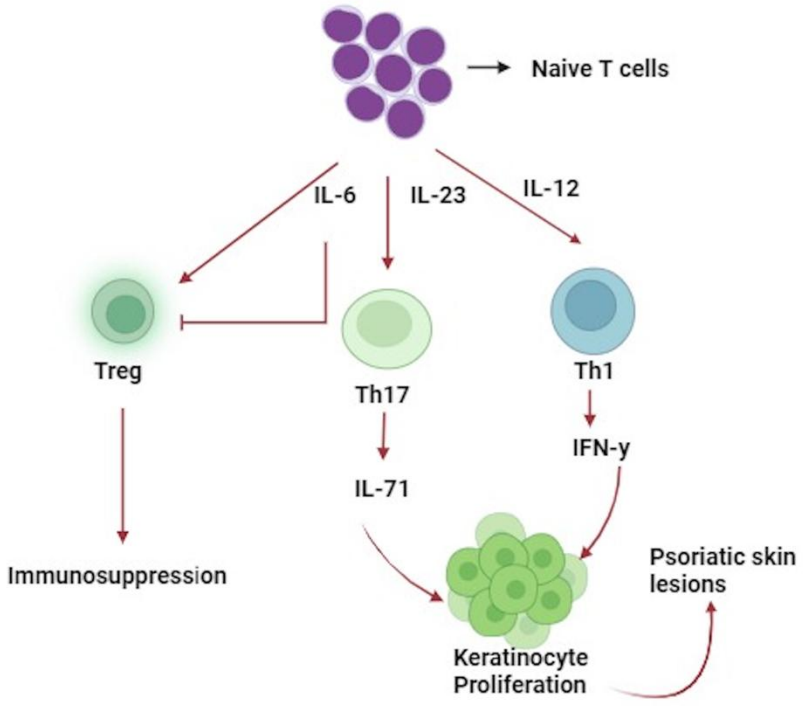

Figure 2: The role of cytokines in the development of psoriatic skin lesions

Furthermore, patients receiving cytokine therapy, such as interferons, frequently report depression as an unwanted side effect.[44-45,56]These clinical observations are corroborated by experimental data from healthy individuals who develop depressive symptoms following peripheral immune challenges induced by vaccination or bacterial endotoxin injection.[57-60]

Several theories have been proposed to explain how elevated pro-inflammatory cytokines might influence neurotransmitter metabolism within the central nervous system (CNS). One theory suggests that patients with major depression have a hyperpermeable blood-brain barrier, allowing serum pro-inflammatory cytokines to enter the CNS. [61] Once present in the CNS, these cytokines can activate neuronal and non-neuronal cells, similar to their mode of action in the peripheral immune system.[62] Another proposed pathway involves the activation of cerebral vascular endothelial cells, leading to the secretion of cytokines inside the blood-brain barrier.[52,63] A third explanatory approach postulates that peripheral inflammatory signals can be transmitted to the CNS via the vagus nerve, as vagus nerve fibers have receptors that can bind serum pro-inflammatory cytokines.[64]

Consequently, peripheral low-grade inflammation is increasingly viewed as a potential therapeutic target in depression. Various studies have investigated the antidepressant efficacy of anti-inflammatory treatments, such as non-steroidal anti-inflammatory drugs (NSAIDs) or cytokine blockers, with some promising results.[45, 47, 65] Further studies assessing the antidepressant effects of IL-6 inhibitors are currently recruiting depressed patients with elevated levels of C-reactive protein (CRP).[66] A comprehensive overview and assessment of anti-inflammatory agents and their potential for antidepressant treatment are available.[67]

Mirroring the broadened conceptualization of depression, psoriasis is no longer viewed as an isolated skin disease. The current understanding considers psoriasis as a systemic inflammatory condition with documented pro-inflammatory reactions that extend beyond the skin.[68] The observation of peripheral inflammation in both psoriasis and depression suggests that this may be one of the shared mechanisms underlying the high rates of psychological comorbidities, particularly depression, in psoriasis patients.

Another link between depression and psoriasis has been found through the substance melatonin. Depression is known to disrupt melatonin release in the body, causing abnormal fluctuations, with elevated levels peaking around 3 am.[69-70] In addition to regulating circadian rhythms and sleep, melatonin can also modulate the immune system, and by decreasing concentrations of TNF-α, IL-6, and IL-8, it may reduce inflammation or mitigate the negative effects of inflammatory cascade byproducts.[70-73] Decreased melatonin levels have been observed in various inflammatory conditions, including psoriasis.[74-75] Furthermore, lowering melatonin levels could exacerbate psoriasis symptoms, as the absence of melatonin in rats has been shown to delay wound healing, an effect that was reversed by melatonin replacement.[76] Treating depression can also restore melatonin to healthy levels and decrease psoriasis

symptomatology.[77] Apart from addressing depression, phototherapy is currently a useful treatment for psoriasis, although the mechanism has not been studied in detail. It is assumed that phototherapy may inhibit keratinocyte production, increase immunomodulation via altered receptor expression, and induce apoptosis of lymphocytes.[78-81] Phototherapy can regulate melatonin levels, alleviate psoriasis symptoms, and potentially mitigate depressive symptoms that may further aggravate psoriasis.[82] Studies have shown that a significant number of individuals with psoriasis associate stress and depressive tendencies with their psoriasis, and a considerable proportion exhibit clinical depression, chronic anxiety, and suicidal thoughts. As such, phototherapy, along with TNF-α blockers that have proven effective in other inflammatory diseases, may be a useful holistic treatment approach.[83-85]

The Role of Inflammation

In light of the theories detailed above, it is relevant to take a closer look at the specific cytokines that play a role in both psoriasis and depression.

Dowlatshahi et al. [86] critically examined the inconsistency of methods, which has led to high heterogeneity in results. Nonetheless, the authors found sufficient evidence to state that levels of the pro-inflammatory cytokines IL-6 and TNF-α are consistently elevated in psoriasis, along with C-reactive protein (CRP), E-selectin, and intercellular adhesion molecule 1 (ICAM-1). These findings are supported by a more recent meta-analysis by Bai et al. [87], although they examined a slightly different array of inflammatory markers and did not assess CRP and ICAM-1. Given the importance of IL-17 in the pathogenesis of psoriasis [88-90], an increased concentration of serum IL-17 might be expected. However, the data remains inconclusive, with some original studies showing elevated IL-17 levels [88], but both negative [86-87] and positive [91] results in meta-analyses.

A comprehensive original study analyzed 157 blood proteins in 266 patients with psoriasis.[92]This study found significant correlations between pre-treatment Psoriasis Area and Severity Index (PASI) and IL-17C, IL-17A, and IL-6. Thus, there is some overlap with the cytokines elevated in depression. However, with only modest differences compared to healthy controls, these immune markers do not qualify as reliable markers of disease severity in psoriasis patients.[86] Following the concept of a shared inflammatory burden as the reason for an overlap in symptoms, it appears likely that there might be a correlation between depressive symptoms and systemic inflammation markers in patients with psoriasis. At least on a clinical level, depression is more prevalent in patients with severe psoriasis, supporting the cytokine hypothesis. However, patients with mild psoriasis can also experience relevant mental health problems.[93-95]

The argument that the overlap between psoriasis and depression is associated with systemic inflammation underlying both conditions would imply that as psychological and psoriatic symptoms improve with therapy, the inflammatory burden should also decrease. No study has directly addressed this so far. However, some studies have investigated the changes in inflammatory markers during anti-psoriatic treatment. One marker that has been repeatedly assessed and found to decrease in levels over the course of treatment is C-reactive protein (CRP) or high-sensitivity CRP (hs-CRP).[96-98] While data on other biomarkers is more heterogeneous, likely due to high variability in study protocols, there is some evidence for a reduction in the levels of several pro-inflammatory cytokines during psoriasis treatment [92, 97-99]. Kim et al. [92] investigated blood serum of patients with moderate-to-severe psoriasis after 4 weeks of treatment with tofacitinib or etanercept and found changes in a wide range of proteins. Among others, IL-6 levels were reduced, while other markers, such as IL-17A, were reduced only in patients with marked skin improvement.

An "indirect" way to assess the influence of systemic anti-psoriatic therapies on inflammatory burden is to examine the cardiovascular risk, as it is known to be closely associated with systemic inflammation.[100-101] In 2015, an initial study investigated the extent to which TNF-α inhibition or methotrexate therapy may have positive effects on cardiovascular risk in patients with rheumatoid arthritis, psoriatic arthritis, and plaque psoriasis, respectively. Limited evidence suggests that these systemic therapies are associated with a decrease in cardiovascular risk.[102] Two years later, Wu et al. [103] expanded the evidence on this issue by demonstrating that cumulative exposure to TNF-α inhibitors was associated with a reduced risk of major cardiovascular events in patients with psoriasis. Later on, data from a prospective observational study showed that biologic therapy (anti-TNF-α, anti-IL12/23, anti-IL17) in severe psoriasis was associated with favorable modulation of coronary plaque indices, as measured by coronary computed tomography angiography.[104] A study specifically investigated the effects of the anti-IL17A antibody secukinumab on cardiovascular risk ("CARIMA" study). Limited evidence was found that secukinumab might have a beneficial effect on cardiovascular risk by improving the endothelial function of patients with plaque psoriasis. [105]

While there is some evidence for the idea of psoriatic inflammation triggering depression, this association appears to be bi-directional.[106] The skin manifestations of psoriasis often worsen with increasing psychological stress, and stressful life events have been shown to play a role in the induction or exacerbation of psoriasis.[94-95,107] This clinical observation is underpinned by experimental data indicating that stress and central nervous system changes can contribute to new onset or exacerbation of psoriasis via a dynamic bidirectional cross-talk between the nervous system and cutaneous immune cells. Through activation of the hypothalamic-pituitary-adrenal axis and the autonomic nervous

system, chronic stress can cause a constant upregulation of the innate pro-inflammatory cytokine profile, including IL-1, IL-6, and TNF-α.[108]

Changes in Psychological Symptoms under Anti-Psoriatic Therapy

Clinical studies on psoriasis investigating different therapeutic agents have shown improvements in the course of depression under anti-inflammatory therapies.[109-113] However, data in this field are relatively scarce, as only a minority of the pivotal studies to date have utilized psychometric scales to assess quality of life in general and depressive symptoms in particular. Studies employing the Dermatological Life Quality Index (DLQI) have consistently demonstrated that systemic therapy, especially with biologic agents, is generally superior to placebo in improving skin-related quality of life.[114-116] These data suggest an improvement in psychological well-being under therapy; however, health-related quality of life (HR-QoL) encompasses more than just symptom reduction, mobility, and time spent on treatment. This is reflected by the finding that one-third of patients who screened positive for depression or anxiety had inconspicuous scores on the DLQI, illustrating the insufficiency of the DLQI as a sole screening tool.[117]

In addition to the DLQI, some pivotal studies included the Short Form Health Survey-36 (SF-36), a generic instrument not specifically tailored for dermatological diseases [118], including subscales analyzing physical and mental well-being, enabling comparison between distinct diseases. The SF-36 mental scores were found to improve after treatment with ustekinumab (PHOENIX) [119], brodalumab compared with placebo (phase-II study) [120], and secukinumab compared with fumaric acid esters ("PRIME" trial).[121] Additionally, a single-arm study also found improvements in the short version SF-12 after treatment with adalimumab.[122]

A common instrument to assess symptoms of anxiety and depression in the clinical context is the Hospital Anxiety and Depression Scale (HADS). This scale was employed, e.g., in the PHOENIX [110], AMAGINE-1 [123], and VOYAGE [110,124] trials, which reported significantly improved symptoms of anxiety and depression over the course of treatment with ustekinumab, brodalumab, and guselkumab, respectively, compared with the placebo groups. The HADS scores also improved in several observational studies without a placebo control group after treatment with adalimumab [122] and etanercept.[125-128] Another well-known measure for assessing depressive symptoms is Beck's Depression Inventory (BDI). This scale was employed in two older studies assessing the efficacy of etanercept [129-130] and reported improved BDI scores over the course of treatment. However, this TNF-α antagonist is rarely prescribed anymore in plaque psoriasis.

So far, no meta-analysis has focused exclusively on the question of improvement in depressive symptoms under anti-inflammatory treatment in patients with psoriasis. However, studies employing different approaches have reported associations between improvement in psoriasis and amelioration of psychological symptoms under biologic therapies.[110,129,131] Additionally, anti-inflammatory treatment has demonstrated an antidepressant effect in patients with inflammatory diseases.[112-113]

CONCLUSION

Recent research has uncovered a link between major depressive disorder (MDD) and the skin condition psoriasis, suggesting shared underlying mechanisms. Studies indicate that psoriasis patients often experience depressive symptoms, and high levels of depression, as defined by DSM standards, can exacerbate psoriasis. However, DSM standards do not fully capture the extent of depression in psoriatic patients, leading to fewer observations of depression in comparative studies.

This review explored literature on the interaction between psoriasis and depression and the impact of anti-psoriatic treatments on depressive symptoms. Depression frequently co-occurs with psoriasis. While it was once believed that stigmatization primarily drove this association, emerging evidence points to overlapping biological mechanisms. Both psoriasis and depression are characterized by elevated levels of proinflammatory cytokines, suggesting inflammation as a potential pathophysiological link.

The close relationship between these conditions makes it challenging to discern whether improvements in depression stem from the direct anti-inflammatory effects of biologics or indirectly from better skin health improving psychological symptoms. Studies have shown improvements in both skin and psychological symptoms with biologic therapy, but these improvements are not always as closely related as one might expect if the reduction in depressive symptoms were purely due to skin improvement. Meta-analyses reveal that anti-cytokine treatments have an antidepressant effect even when the somatic disease does not respond, suggesting a direct effect of the biologics.

Clinical trials have demonstrated that anti-inflammatory agents, such as TNF-α antagonists, have antidepressant effects, and new treatments targeting inflammatory mechanisms, like IL-6 inhibitors, are being developed. To better compare changes in psychological symptoms across different anti-psoriatic treatments, there needs to be consensus on specific depression screening tools. Regular screening for comorbid depression should also be standardized and implemented in dermatological practice to reduce the psychological burden associated with psoriasis.

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