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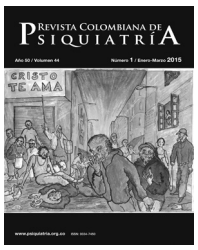

Review article

Pro-inflammatory Cytokines, Biomarkers, Genetics and the Immune System: A Mechanistic Approach of Depression and Psoriasis

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ABSTRACT

Objective: To highlight the inflammatory and immunological mechanisms involved in depression and psoriasis.
Methods: A comprehensive literature search was performed in various databases, in total 145 studies were selected.
Results: Depression and psoriasis have an association. Immune mechanisms —the actions of tumor necrosis factor-α, interleukin 1 (IL-1), IL-2, IL-10, IL-22, IL-17, interferon-γ, IL-1β, prostaglandin E2, C-reactive protein, IL-6, and IL-8 etc.—, and some genetic changes are involved.
Conclusions: A possible bidirectional relationship of psoriasis and major depression exists; i.e. the depression leads to psoriasis, and psoriasis leads to depression. We recommend more studies in the future to get a deeper and better understanding about this relationship.

Citocinas proinflamatorias, biomarcadores, genética y sistema inmunológico: un enfoque mecanicista de la depresión y la psoriasis

Palabras clave:
Depresión por psoriasis
Psicodermatología
Neurodermatología
Psoriasis y depresión mayor
Depresión por inflamación
Inflamación por psoriasis

RESUMEN

Objetivo: Poner de relieve los mecanismos inflamatorios e inmunológicos involucrados en la depresión y la psoriasis.
Métodos: Se realizó en varias bases de datos una búsqueda bibliográfica completa; en total se incluyeron 145 estudios.
Resultados: Hay asociación entre depresión y psoriasis y están involucrados mecanismos inmunitarios —las acciones del factor de necrosis tumoral alfa, las interleucinas (IL) 1, 2, 10, 22 y 17, el interferón gamma, la IL-1β, la prostaglandina E2, la proteína C reactiva, la IL-6 y la IL-8, etc.— y algunos cambios genéticos.

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Conclusiones: Hay una posible relación bidireccional entre psoriasis y depresión, es decir, la depresión lleva a psoriasis y la psoriasis lleva a depresión. Se recomiendan más estudios en el futuro para obtener una comprensión más profunda y mejor sobre esta relación.

Introduction

"Doctor! I have been treated for major depression for the past so many years and now I have developed this silvery skin." These kinds of statements are occasionally heard in the psychiatric settings. The similar kinds of complaints are brought to a dermatological clinic, where patients with skin problems complain of depressed moods. These kinds of cases are the classic examples of psycho-dermatological phenomenon,[1] which is a sub-branch of psychosomatic medicine.[2] The effects of behavioral, social, and psychological factors on the bodily processes and their relationship with each other are studied in psychosomatic medicine.[2] In this review article, we emphasize on psycho-dermatological relationship between psoriasis and major depression.

Any disorder that involves an interaction between the brain and the skin is classified as a psycho-dermatological disorder. Three common kinds of psycho-dermatological disorders have been described so far, that includes: psycho-physiologic disorders, primary psychiatric disorders, and secondary psychiatric disorders.[3] The subject of the association of skin and brain is well studied in the recent past. Moreover, the relationship between depression and psoriasis is also studied in relation to psycho-dermatology. Today, we do know that psoriasis can cause major depression, its bi-directionality (depression leading to psoriasis) is not fully understood yet. The ideas that "major depression leads to psoriasis, any cutaneous damage associated with major depression that causes psoriasis, or any inflammatory markers or cytokines released in depressed patient's brain or body that can initiate psoriasis" is not much discussed. In this article we will highlight the answers to the above mentioned statements.

The mechanism of depression has been studied in depth, and its association with various neurochemicals has been suggested. Depression is known to have an effect on the integumentary system and other organ-systems, like the cardiovascular system.[4–8] Similarly, psoriasis is a chronic, immune mediated inflammatory disease of skin that leads to red, itchy plaques (white/silver) on the skin.[9] Naturally, having such a severe cosmetic disease can affect the patient's mental health and may lead to depression. However, it could also be a consequence of major depression, due to an immunological and a neurochemical phenomenon.[10]

In this review, we will discuss the association of the human brain with the human body's immune system; inflammatory mechanism involved in the pathophysiology of psoriasis, inflammation and its relationship with major depression, and how both of these conditions could be related and augment each other; possibly due to a bidirectional mechanism. We will conclude the article with the future research recommendations.

Immune System and the Brain

Heightened keratinocyte proliferation and leukocyte invasion into the uppermost layers of skin during inflammation that characterizes the disease known as psoriasis, causing the formation of physical pathology, has recently been found to be associated with psychological disorders such as depression through the mechanisms revolving the immune system.[10] Statistically speaking, significant evidence in the previous decades have suggested an association between clinically diagnosed depression, or depressive factors, and skin diseases including psoriasis on multiple occasions. In a study done by Esposito et al.[11] on 2391 patients, depressive indicators were present in 62% of the sample size. The presence of psoriasis in individuals, and its respective severity, has also been found to be linked with increased depressive symptomatology in a study done in 2002, where psoriatic patients were found to have even higher depressive "scores" than non-psoriasis afflicted depressed patients.[12] Topping it however, Gupta et al.[13,14] on two occasions observed that elevation in psychosocial impairment related to depression and stress strongly correlated to psoriasis morbidity and the onset of physical pathology. Reduction in psoriatic clinical morbidity due to medical or other treatment has also been linked to reduced depressive symptoms, with the converse true as well, in multiple studies.[15–21] However, as with any apparent dermatological, or even non dermatological disorder for that matter, the antisocial, emotional, self-esteem lowering, anxiousness, and other factors that affect the psychological health of an individual are strong possibilities as to why depressive symptoms are effected and the data above is observed, but this does not explain the converse and this paper supports the idea that there is an even stronger connection between the immune system and the brain not yet fully explored.

Inflammatory Mechanism of Psoriasis

The presence of keratinocytes, leukocytes, T cells, macrophages, and dendritic cells and their migratory pathways towards the epidermis, the outermost layer of skin, and away from the inner layers, followed by the release of inflammatory cytokines including interleukin (IL) 1β, and IL-6, IL-22, tumor necrosis factor-α, (TNF-α) or a type-1 cytokine profile (IL-2, interferon [IFN] γ, and TNF-α) has been observed to be the cause of psoriasis, or more specifically psoriatic lesions.[22,23] IL-6 and other cytokines are thought to influence maturation of T cells into Th17 cells, pulling neutrophils to specified location.[24] IFN-γ and TNF-α levels may also be elevated from either Th1[25] or Th17 cells,[26] and further amplify

inflammation. The release of the cytokines IL-1, IL-6, and TNF-α due to dendritic and T cell activity initiate inflammatory pathways with trigger further inflammation, and deficiencies in inhibitory or regulatory IL-10 and T cells may be what allows for this to happen.[27] Dendritic cells which activate the usage of antigen-specific adaptive immunity by acting as messengers of the innate immune system are thought to act as the first step in the physical formation of psoriatic lesions though these systems[28] resulting in inflammatory upregulation that causes hyperproliferation of keratinocytes.[29,26,30,31] The hyperproliferation of keratinocytes and respective cell activity is greater than standard cell activity, even during injury or healing,[32] and causes 6 to 10 times faster skin replacement, without proper removal through standard practices, i.e. shedding.[33] However, although mutations in regulatory cells are thought to be the cause of such phenomena the downstream effects are not particularly distinct from the standard inflammatory response.[34]

The term "diffuse brain[35]" has often been used to describe the highly innervated skin coining its strong relation to psychoneurological factors. The skin is known to contain a wide variety of neuropeptides including calcitonin gene-related peptide (CGRP), vasoactive intestinal peptide (VIP), nerve growth factor (NGF), substance P, and catecholamines, and studies have found a correlation between autonomic nervous system and respective neuropeptide activation with psoriasis.[36,37] In fact, in patients with severance of sensory innervation due to trauma in specific areas, psoriatic plaques in those areas receded, coming back after nerve healing had occurred.[38] This finding supports the idea that neuropeptides and brain activity relating to the release of said peptides may factor into the longevity of psoriasis or even its onset.[38,39] Psoriatic plaques have also been found to have increased nerve fiber density and abnormal expression of various neuropeptides,[39–42] and this finding is substantiated due to the fact that increased concentration of NGF and other neuropeptides mediate T cell and keratinocyte proliferation, memory T cell chemotaxis, mast cell migration, and degranulation, all processes known to be related to psoriatic lesions.[39–44] Additionally, blood brain-derived neurotropic factor (BDNF) is found to be significantly reduced in psoriatic and depressive patients.[45] As such, it can be said that the inflammation pathway that includes TNF-α, IFN-γ, and other type-1 cytokines strongly delineates the mechanism underlying psoriasis,[21] however certain other forces may be at play and this mechanism may not just be limited to local skin areas. Furthermore, IL-17 has also been considered relevant with respect to psoriasis pathophysiology.[46–48]

Inflammatory Mechanism of Depression

Extensive amounts of data now exist that highlight the role of inflammation in individuals suffering from depression or chronic stress including but not limited to activation of cell-mediated immunity, compensatory anti-inflammatory reflex system, negative immunoregulatory processes and chronic inflammatory responses.[49,50] IL-21, IL-17, and transforming growth factor β (TGF–β) are found in the people suffering from major depressive disorder.[51]

Specifically, increased levels of IP-10, or CXCL10, factors known to be involved in the localization of T cells, dendritic cells, and macrophages,[52,53] were found in depressed patients, with antidepressants such as SSRIs lowering concentration, and increasing production of anti-inflammatory cytokines.[54–56] Interestingly, changes in leukocyte mRNA expression, mRNA coding for cyclooxygenase-2, myeloperoxidase, inducible nitric oxide synthase and secretory phospholipase A2 type IIA, have been observed in chronically depressed patients, with inflammatory gene expression lowering 8 weeks after treatment.[57,58] Peripheral blood inflammatory biomarkers have also been shown to have an association with neural plasticity, neurotransmitter metabolism, and neuroendocrine function, in areas directly related to depression.[59] Persistently elevated inflammatory biomarkers have been found in depressed patients leading to chronic damage due to increased oxidative and nitrosative stress, and increased stimulation of signal molecules related to inflammation like NF-κB through activation of the sympathetic nervous system and respective outflow pathways.[59–62] This chronic inflammation indepedently has also been shown to be associated with the presence of depression and other psychological disorders.[63] Remission of clinical depression through antidepressant treatment has shown normalization of inflammation related substances.[64,65]

An almost direct dose response has been found between the severity of depression/depressive symptoms and the concentration of proinflammatory cytokines such as TNF-α, IL-1β, IL-2, IL-6, prostaglandin E2, and C-reactive protein (CRP).[63,66] Additionally, *in vivo* studies in animals have shown the onset of depressive symptoms and "sickness behavior" after introduction of proinflammatory cytokines, affecting serotonin concentration and availability and even triggering clinical depression.[67] Psychological stressors, including inescapable foot shock, immobilization, and tail restraint, have also been shown to cause significant increases in IL-1 (mRNA) levels in the plasma and brain, with downstream production of NF-κB, activation of prostaglandin and cyclooxygenase 2 production, and increased cell apoptosis.[68–74] TNF-α has been thought to be linked to greater 5-HTT availability with TNF-α inhibition decreasing 5-HTT availability.[10] Many studies have shown increased acute-phase proteins, increased expression of chemokines and adhesion molecules, and increased proinflammatory cytokines in patients with depression, without the existence of any preexisting inflammatory disorders.[75–91] Abnormal concentration of IL-1-β and TNF-α can be seen as well in both the cerebrospinal fluid and peripheral blood circulation in patients with the symptoms of depression.[99,52,100,101] Moreover, treatment of disorders, such as hepatitis C, with interferon alpha has shown to induce clinically defined major depression in almost 50% of patients highlighting the necessity in understanding the key factors that may be involved in diseases, such as inflammation in depression.[92–98]

Physiological Connections

The presence of inflammation in both psoriasis and depression and the specificity in the inflammatory pathways and respective biomarkers that has observed clearly marks the

Table 1 – Showing some relevant studies about the association of depression and psoriasis.

Author/Publication year	Country	Study Design	Population	Sample Size	Diagnostic Criteria	Main Points
Van Beelen et al.[24], 2007	Netherlands	Review	N/A	N/A	N/A	Unique subset of interleukin (IL)-17-producing CD4+ T helper (Th17) cells, distinct from Th1 and Th2 cells discovered and association to inflammatory skin diseases studied. Th17 cells are found to be involved in protection against bacterial pathogens, in addition to being crucial in the pathogenesis of various chronic inflammatory diseases that were formerly categorized as Th1-mediated disorders.
Zheng et al.[25], 2007	USA	Review	N/A	N/A	N/A	Results suggest that T(H)17 cells, through the production of both IL-22 and IL-17, might have essential functions in host defence and in the pathogenesis of autoimmune diseases such as psoriasis. IL-22, as an effector cytokine produced by T cells, mediates the crosstalk between the immune system and epithelial cells.
Lowes et al.[26], 2008	USA	Longitudinal Study	Healthy volunteers skin (n=4), abdominoplasty normal skin (n=4), moderate to severe psoriasis patients skin(n=4), psoriasis patients (n=11)	12 skin samples, 11 patients	Unspecified	IL-17 mRNA increased with disease activity, and IL-17 mRNA expression normalized with cyclosporine therapy. IL-22 mRNA expression mirrored IL-17 and both were downregulated in parallel with keratin 16. Th17 cells are a discrete population, separate from Th1 cells (which are also in psoriasis lesions), and Th2 cells. Our findings suggest that psoriasis is a mixed Th1 and Th17 inflammatory environment. Th17 cells may be proximal regulators of psoriatic skin inflammation, and warrant further attention as therapeutic targets.
Vissers et al.[31], 2004	USA	Longitudinal Study	patients with chronic plaque psoriasis	7 psoriasis patients	Unspecified	Calcipotriol proved to have a major effect on the proliferation marker Ki-67 and differentiation marker keratin-10, whereas the effect on T-cell subsets was more selective with major reductions of CD45RO(+) and CD8(+) T cells. In contrast, the effect of betamethasone dipropionate on the epidermis was restricted to a normalization of differentiation with a highly significant increase of keratin-10 positive epidermal surface without a significant effect on Ki-67 positive nuclei, and the effect on T-cell subsets was restricted to a reduction of natural killer T-cell receptors designated by CD94 and CD161 in the epidermis. The combination of the two treatments did not affect the proliferation marker Ki-67 and keratinization marker keratin-10, beyond the effect of calcipotriol monotherapy. However, the combination had a profound effect on, virtually, all T-cell subsets, beyond the effect of the monotherapies.
Urpe et al.[35], 2005	USA	Review	N/A	N/A	N/A	There is clinical and experimental evidence that the brain can start, influence, and stop biologic skin events. Studies suggest that the skin, as a relevant part of the “diffuse brain,” can modify the quality of perceptions and feelings. The immune and the endocrine systems seem to represent the protagonists of the modulation of those events and, in this context, psychosocial stressors and interventions can lead to global health changes of great interest for dermatologists.
Farber et al.[38], 1990	USA	Cross Sectional Study	Chronic plaque psoriasis patients in whom cutaneous nerve damage resulted in clearance of the disease at that site	2 patients	Unspecified	Nerve damage resulted in clearance of psoriasis at that site. In both patients reappearance of the psoriasis occurred with recovery of cutaneous sensation. The role of cutaneous sensation in the maintenance of skin disorders and, in particular, the role of neuropeptides in the pathogenesis of psoriasis are discussed.
Angiolillo et al.[53], 1995	USA	Longitudinal Study	6-wk-old female BALB/c nu/nu mice	4 mice and mice cell cultures	Unspecified	IP-10 is a potent inhibitor of angiogenesis in vivo. IP-10 profoundly inhibited basic fibroblast growth factor-induced neovascularization of Matrigel (prepared by H.K. Kleinman) injected subcutaneously into athymic mice. In addition, IP-10, in a dose-dependent fashion, suppressed endothelial cell differentiation into tubular capillary structures in vitro. IP-10 had no effect on endothelial cell growth, attachment, and migration as assayed in vitro. These results document an important biological property of IP-10 and raise the possibility that IP-10 may participate in the regulation of angiogenesis during inflammation and tumorigenesis.

existence a physiological relationship.[99] Depression and psoriasis can be said to be statistically and biologically linked, and in fact certain studies have found the existence of specific tandem repeat polymorphisms in intron 2 of the 5-HTT gene and serotonin receptors related genes, which may underlie phenomena present in individuals with psoriatic lesions.[99] Many dermatological issues have been shown to have a number of comorbidities with psychiatric and other illnesses, with psoriasis specifically having links to anxiety and depression, inflammatory bowel disease, fatty liver, cancer, diabetes, hypertension, dyslipidemia, cardiovascular disease, and other inflammatory or metabolic-related sickness.[52] Prevalence of inflammation related diseases was found to be significantly higher in psoriatic patients, and vaccination related immune responses could elicit depressive symptoms regardless of observable physical sickness.[100] Specifically in rats, injection of lipopolysaccharide (LPS) and IL-1 (an inflammatory cytokine) caused behavioral changes including decreases in interest exploring, sleep, energy, sexual activity, and appetite, changes that often predate clinical depression.[101,102] Additionally, CRP and IL-6 measurements were observed to correlate to the onset of future depression in a 12-year study.[102]

Direct causal relations between depression and psoriasis have been difficult to ascertain, however, there is evidence that mechanisms leading to each other are at play. In a study by Capuron et al., it was observed that inflammatory cytokine release, associated with psoriasis, directly increased the activation of indoleamine 2,3-dioxygenase, the enzyme responsible for converting tryptophan to kynurenine.[103] Tryptophan is a precursor to serotonin, with kynurenine production effectively decreasing serotonin concentration, and this coupled with the effect of tryptophan metabolism, can independently lead to signs of depression, and glucocorticoids associated with inflammation can also activate this pathway.[104] Increased breakdown of serotonin may also be caused by the presence of inflammatory cytokines, and serotonin breakdown can lead to depressive symptoms.[105] It is also hypothesized that HPA axis hyperactivity associated with clinical depression can be caused by increased concentrations of inflammatory factors, negatively affecting the feedback inhibition pathway of corticosteroids and lowering serotonin/serotonergic neurotransmitter activity, inducing peripheral cell-mediated activation, activating oxidative and nitrosative stress pathways, increasing central microglial activity, decreasing neuron formation, increasing cell death, and effecting melancholy, anxiety, fatigue, and eventually depression.[101,106] Interestingly, systemic increases in inflammation/inflammatory response are associated with depression, which often precede onset of psoriasis symptoms, and this inflammation may increase psoriatic morbidity.[107–109] Risk of developing psoriasis has also been shown to be significantly higher in depressed patients, corroborating this finding.[110–112] Additionally, CRP has been present in depressed patients with levels at times showing a dose response with depressive morbidity[113] and predecessors of depression, such as stress, have been shown to have an association with CRP levels in psoriatic women, with stress causing phenotypic changes in patients.[114,115]

Another link between depression and psoriasis has been found through the substance known as melatonin. Depression is known to disrupt melatonin release in the body, causing it to no longer function as normal, with elevated levels at night peaking around 3 am.[116,117] However, aside from the regulation of normal circadian rhythm and sleep, melatonin can also regulate the immune system, and by decreasing concentrations of TNF-α, IL-6, and IL-8 may reduce inflammation or decrease the negative effects of inflammatory cascade byproducts.[117–120] Decreased melatonin levels have been observed in a number of inflammatory conditions, with psoriasis included.[121,122] Additionally, lowering of melatonin levels could increase symptoms of psoriasis, as absence of melatonin in rats was shown to delay wound healing, with melatonin replacement undoing said phenomena.[123] Treatment of depression can also return melatonin to healthy concentrations and decrease psoriasis symptomology.[124] Aside from treating depression, phototherapy is currently a useful treatment for psoriasis and although the mechanism has not been studied in detail, it is assumed that it may inhibit keratinocyte production, increase immunomodulation via altered receptor expression, and cause apoptosis of lymphocytes.[125–128] Phototherapy can regulate melatonin levels, decrease psoriasis symptoms, and lessen depressive symptoms that further aggravate psoriasis.[129] Studies have shown that a significant number of individuals with psoriasis liken stress and depressive tendencies to their psoriasis, and a significant amount are found with clinical depression, chronic anxiety, and suicidal thoughts, and as such phototherapy may be a useful holistic treatment, along with TNF-α blockers that have found use in other inflammatory diseases.[130–132]

Aside from biomarkers, a study done in 2012 indicates the potential of a genetic connection between depression and psoriasis.[133] Utilizing methods such as G-banding and cell cultivation, changes in chromosomes 8, 15, 21, 22, and the sex chromosomes were observed in a family with both psoriasis and manic depression. Del(1)(q12-q23), del(1)(q21.1-q24), del(1)(q21.1-q23), del(10)(p11.2-pter), der(2)t(2;4)(p25;p12), t(2;22)(p14;p13), t(19;Y)?, and dup(10)(q26) were found as compared to healthy individuals indicating the potential presence of psoriasis/depression genes. Additionally chromosomal changes of 4 with 45,X (5.8%), 3 with 47,XXY (4.3%), and 4 with structural chromosome X (5.8%): del(X)(q13), del(X)(p11-pter), del(X)(q21.3), and inv(Y)(q11.2), were found. These changes were also linked to increased amounts of CD2+, CD4+, and CD8+ in the father, CD4+ reductions in the mother, and CD4+ reductions in the son with increased CD8+. Compared to average the CD4/CD8 ratio of the son and the father was significantly higher than normal implying either a genetic disposition or the damaging effect of psoriasis and depression on genes/inflammatory biomarkers.[134]

Clinical depression is known to have a strong connection with suicidal thoughts, tendencies, and actions, however, controversy exists surrounding the potential association of psoriasis and suicide.[135,136] Previously, it has been assumed that interleukin-17R blockade utilized in the treatment of psoriasis may have an effect on suicidal ideation, but empirical evidence supporting this claim is limited.[137] Psoriasis is also associated with alexithymia and anxiety.[138] However, this subject warrants its own article. Moreover, the treatment

of psoriasis especially with the co-existent depression can be challenging to treat. Because some medications do either worsen or trigger psoriasis. Medication used in the treatment of a wide variety of illnesses including blood pressure medications, anti-malarial drugs, NSAIDs, lithium, fluoxetine, amiodarone and other heart related medicine, however, has been found to increase psoriatic morbidity.[139–141] As such, it is essential for healthcare professionals to consider the side effects of such treatment associated with some of the common comorbidities of psoriasis, and the potential relationship between psoriasis and other phenomena when dealing with psoriatic patients. (Table 1)

Conclusions

Recent evidence that has been compiled on the topic of major depressive disorder and the skin disorder, psoriasis, suggests that there is indeed a link between the two in regards to their respective underlying mechanisms. In fact, studies have shown that patients suffering from psoriasis, or more specifically the symptoms of psoriasis, often have depressive tendencies and elevated levels of depression, as per DSM standards, may lead to heightened effects of psoriasis. When it comes to issues such as depression, however, DSM standards are not wholly inclusive and as such data regarding depressed psoriatic patients is limited, highlighted in fewer depression observations in comparison studies. Abnormal concentrations of a number of different chemicals have been associated with depression, including melatonin, and this has also been found in psoriatic patients, with incredibly low concentrations present in individuals with both depression and psoriasis. Interestingly, chemical regulation, specifically regarding melatonin, has had positive effects on depressed psoriasis patients in terms of reducing disease morbidity. Although it is known that in many patients with skin disorders there exists an extensive emotional burden, depression and psoriasis have actually been found to be more closely linked through inflammation. Many of the inflammatory molecules and signals that move towards the uppermost layers of skin and create lesions observed in psoriasis, causing the initial formation of said lesions or increasing the multitude of observable lesions, have also been found to be at higher levels in depressed patients. These molecules, increasing in concentration due to psoriasis, can also cross the blood brain barrier and impact mental state, or interfere with proper functioning of the brain circuitry that is related to depressive symptoms and the onset of major depressive disorder. Inflammation related hypothalamic-pituitary-adrenal axis hyperactivity may also lower 5-HT and serotonergic neurotransmitter levels further impacting mental state. Despite all this however, phototherapy has been found to reduce both depressive and psoriatic symptoms. Antidepressant therapy may also reduce psoriasis and anti-inflammation medication used in psoriasis may decrease clinical depression. As such, due to the similarity in the presence of inflammatory molecules and signals and mechanisms by which these molecules function there is significant evidence that a relationship between depression and psoriasis exists. However this relationship warrants further study as specific phenomena or biological substances indicative of disease or present in depression are not necessarily found in skin disorders such as psoriasis with the converse also being true. Additionally, psoriasis is not always present in patients with depression and depressive symptomology is not necessarily present in psoriasis patients indicating the possibility of additional factors being at play.

Conflicts of interests

None.

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REFERENCES

1. Brown GE, Malakouti M, Sorenson E, Gupta R, Koo JY. Psychodermatology. Adv Psychosom Med. 2015;34:123–34.
2. Levenson JL. Essentials of psychosomatic medicine. Arlington: American Psychiatric Press; 2006.
3. Leon A, Levin EC, Koo JY. Psychodermatology: an overview. Semin Cutan Med Surg. 2013;32:64–7.
4. White JR, Chang CH, So-Armah KA, Stewart JC, Gupta SK, Butt AA, et al. Depression and HIV Infection are Risk Factors for Incident Heart Failure Among Veterans: Veterans Aging Cohort Study. Circulation. 2015;132:1630–8.
5. Bisschop MI, Kriegsman DM, Deeg DJ, Beekman AT, van Tilburg W. The longitudinal relation between chronic diseases and depression in older persons in the community: the Longitudinal Aging Study Amsterdam. J Clin Epidemiol. 2004;57:187–94.
6. Krishnan KR, Delong M, Kraemer H, Carney R, Spiegel D, Gordon C, et al. Comorbidity of depression with other medical diseases in the elderly. Biol Psychiatry. 2002;52:559–88.
7. Nicholson A, Kuper H, Hemingway H. Depression as an aetiologic and prognostic factor in coronary heart disease: a meta-analysis of 6,362 events among 146,583 participants in 54 observational studies. Eur Heart J. 2006;27:2763–74.
8. Nasir U, Shahid H, Shabbir MO. Sleep quality and depression in hospitalized congestive heart failure patients. J Pak Med Assoc. 2015;65:264–9.
9. Questions and Answers about Psoriasis. National Institute of Arthritis and Musculoskeletal and Skin Diseases; 2013. Available from: http://www.niams.nih.gov/health_info/psoriasis/.
10. Krishnadas R, Nicol A, Sassarini J, Puri N, Burden AD, Leman J, et al. Circulating tumour necrosis factor is highly correlated with brainstem serotonin transporter availability in humans. Brain Behav Immun. 2016;51:29–38.
11. Esposito M, Saraceno R, Giunta A, Maccarone M, Chimenti S. An Italian study on psoriasis and depression. Dermatology. 2006;212:123–7.
12. Akay A, Pekcanlar A, Bozdag KE, Altintas L, Karaman A. Assessment of depression in subjects with psoriasis vulgaris and lichen planus. J Eur Acad Dermatol Venereol. 2002;16:347–52.
13. Gupta MA, Gupta AK, Kirkby S, Schork NJ, Gorr SK, Ellis CN, et al. A psychocutaneous profile of psoriasis patients who

are stress reactors. A study of 127 patients. Gen Hosp Psychiatry. 1989;11:166–73.
14. Gupta MA, Gupta AK, Schork NJ, Ellis CN. Depression modulates pruritus perception: a study of pruritus in psoriasis, atopic dermatitis, and chronic idiopathic urticaria. Psychosom Med. 1994;56:36–40.
15. Fordham B, Griffiths CE, Bundy C. A pilot study examining mindfulness-based cognitive therapy in psoriasis. Psychol Health Med. 2015;20:121–7.
16. Polenghi MM, Molinari E, Gala C, Guzzi R, Garutti C, Finzi AF. Experience with psoriasis in a psychosomatic dermatology clinic. Acta Derm Venereol Suppl (Stockh). 1994;186:65–6.
17. Menter A, Augustin M, Signorovitch J, Yu AP, Wu EQ, Gupta SR, et al. The effect of adalimumab on reducing depression symptoms in patients with moderate to severe psoriasis: a randomized clinical trial. J Am Acad Dermatol. 2010;62:812–8.
18. Fortune DG, Richards HL, Kirby B, Bowcock S, Main CJ, Griffiths CE. A cognitive-behavioural symptom management programme as an adjunct in psoriasis therapy. Br J Dermatol. 2002;146:458–65.
19. Mease PJ, Signorovitch J, Yu AP, Wu EQ, Gupta SR, Bao Y, et al. Impact of adalimumab on symptoms of psoriatic arthritis in patients with moderate to severe psoriasis: a pooled analysis of randomized clinical trials. Dermatology. 2010;220:1–7.
20. Redighieri IP, Maia Tde C, Nadal MA, Caliman TR, Ruiz Mde F, Petri V. Erythrodermic psoriasis with regression after prophylaxis with isoniazid and antidepressant therapy: case report. An Bras Dermatol. 2011;86 4 Suppl 1:S141–3.
21. Van Voorhees AS, Fried R. Depression and quality of life in psoriasis. Postgrad Med. 2009;121:154–61.
22. Palfreeman AC, McNamee KE, McCann FE. New developments in the management of psoriasis and psoriatic arthritis: a focus on apremilast. Drug Des Devel Ther. 2013;7:201–10.
23. Cedeno-Laurent F, Gómez-Flores M, Mendez N, Ancer-Rodríguez J, Bryant JL, Gaspari AA, et al. New insights into HIV-1 primary skin disorders. J Int AIDS Soc. 2011;14:5.
24. van Beelen AJ, Teunissen MB, Kapsenberg ML, de Jong EC. Interleukin-17 in inflammatory skin disorders. Curr Opin Allergy Clin Immunol. 2007;7:374–81.
25. Zheng Y, Danilenko DM, Valdez P, Kasman I, Eastham-Anderson J, Wu J, et al. Interleukin-22, a T(H)17 cytokine, mediates IL-23-induced dermal inflammation and acanthosis. Nature. 2007;445:648–51.
26. Lowes MA, Kikuchi T, Fuentes-Duculan J, Cardinale I, Zaba LC, Haider AS, et al. Psoriasis vulgaris lesions contain discrete populations of Th1 and Th17 T cells. J Invest Dermatol. 2008;128:1207–11.
27. Nestle FO, Kaplan DH, Psoriasis Barker J. N Engl J Med. 2009;361:496–509.
28. Ouyang W. Distinct roles of IL-22 in human psoriasis and inflammatory bowel disease. Cytokine Growth Factor Rev. 2010;21:435–41.
29. Uyemura K, Yamamura M, Fivenson DF, Modlin RL, Nickoloff BJ. The cytokine network in lesional and lesion-free psoriatic skin is characterized by a T-helper type 1 cell-mediated response. J Invest Dermatol. 1993;101:701–15.
30. Korver JE, van Duijnhoven MW, Pasch MC, van Erp PE, van de Kerkhof PC. Assessment of epidermal subpopulations and proliferation in healthy skin, symptomless and lesional skin of spreading psoriasis. Br J Dermatol. 2006;155:688–94.
31. Vissers WH, Berends M, Muys L, van Erp PE, de Jong EM, van de Kerkhof PC. The effect of the combination of calcipotriol and betamethasone dipropionate versus both monotherapies on epidermal proliferation, keratinization and T-cell subsets in chronic plaque psoriasis. Exp Dermatol. 2004;13:106–12.
32. Raychaudhuri SK, Maverakis E, Raychaudhuri SP. Diagnosis and classification of psoriasis. Autoimmun Rev. 2014;13:490–5.
33. Parrish L. Psoriasis: symptoms, treatments and its impact on quality of life. Br J Community Nurs. 2012;17:524,526,528.
34. Nestle FO, Kaplan DH, Barker J. Psoriasis. N Engl J Med. 2009;361:496–509.
35. Urpe M, Buggiani G, Lotti T. Stress and psychoneuroimmunologic factors in dermatology. Dermatol Clin. 2005;23:609–17.
36. Halevy S, Livni E. Beta-adrenergic blocking drugs and psoriasis: the role of an immunologic mechanism. J Am Acad Dermatol. 1993;29:504–5.
37. Steinkraus V, Steinfath M, Stove L, Korner C, Abeck D, Mensing H. Beta-adrenergic receptors in psoriasis: evidence for down-regulation in lesional skin. Arch Dermatol Res. 1993;285:300–4.
38. Farber EM, Lanigan SW, Boer J. The role of cutaneous sensory nerves in the maintenance of psoriasis. Int J Dermatol. 1990;29:418–20.
39. Raychaudhuri SP, Farber EM, Raychaudhuri SK. Role of nerve growth factor in RANTES expression by keratinocytes. Acta Derm Venereol. 2000;80:247–50.
40. Farber EM, Nall L. Psoriasis: a stress-related disease. Cutis. 1993;51:322–6.
41. Farber EM, Nickoloff BJ, Recht B, Fraki JE. Stress, symmetry, and psoriasis: possible role of neuropeptides. J Am Acad Dermatol. 1986;14 2 Pt 1:305–11.
42. Nickoloff BJ, Schroder JM, von den DP, Raychaudhuri SP, Farber EM, Boehncke WH, et al. Is psoriasis a T-cell disease? Exp Dermatol. 2000;9:359–75.
43. Raychaudhuri SP, Jiang WY, Smoller BR, Farber EM. Nerve growth factor and its receptor system in psoriasis. Br J Dermatol. 2000;143:198–200.
44. Aloe L, Alleva E, Fiore M. Stress and nerve growth factor: findings in animal models and humans. Pharmacol Biochem Behav. 2002;73:159–66.
45. Brunoni AR, Lotufo PA, Sabbag C, Goulart AC, Santos IS, Benseñor IM. Decreased brainderived neurotrophic factor plasma levels in psoriasis patients. Braz J Med Biol Res. 2015;48:711–4.
46. Owczarczyk-Saczonek A, Placek W. Interleukin-17 as a factor linking the pathogenesis of psoriasis with metabolic disorders. Int J Dermatol. 2017;56:260–8.
47. Campa M, Menter A. A review of emerging IL-17 inhibitors in the treatment of psoriasis focusing on preclinical through phase II studies. Expert Opin Investig Drugs. 2016;25:1337–44.
48. Wasilewska A, Winiarska M, Olszewska M, Rudnicka L. Interleukin-17 inhibitors. A new era in treatment of psoriasis and other skin diseases. Postepy Dermatol Alergol. 2016;33:247–52.
49. Maes M. Evidence for an immune response in major depression: a review and hypothesis. Prog Neuropsychopharmacol Biol Psychiatry. 1995;19: 11–38.
50. Maes M, Berk M, Goehler L, Song C, Anderson G, Gałecki P, et al. Depression and sickness behavior are Janus-faced responses to shared inflammatory pathways. BMC Med. 2012;10:66.
51. Davami MH, Baharlou R, Ahmadi Vasmehjani A, Ghanizadeh A, Keshtkar M, Dezhkam I, et al. Elevated IL-17 and TGF-β Serum Levels: A Positive Correlation between T-helper 17 Cell-Related Pro-Inflammatory Responses with Major Depressive Disorder. Basic Clin Neurosci. 2016;7:137–42.
52. Dufour JH, Dziejman M, Liu MT, Leung JH, Lane TE, Luster AD. IFN-gamma-inducible protein 10 (IP-10; CXCL10)-deficient mice reveal a role for IP-10 in effector T

cell generation and trafficking. J Immunol. 2002;168:3195–204.
53. Angiolillo AL, Sgadari C, Taub DD, Liao F, Farber JM, Maheshwari S, et al. Human interferon-inducible protein 10 is a potent inhibitor of angiogenesis in vivo. J Exp Med. 1995;182:155–62.
54. Wong ML, Dong C, Maestre-Mesa J, Licinio J. Polymorphisms in inflammation-related genes are associated with susceptibility to major depression and antidepressant response. Mol Psychiatry. 2008;13:800–12.
55. Xia Z, DePierre JW, Nassberger L. Tricyclic antidepressants inhibit IL-6, IL-1 beta and TNF-alpha release in human blood monocytes and IL-2 and interferon-gamma in T cells. Immunopharmacology. 1996;34:27–37.
56. Maes M, Song C, Lin AH, Bonaccorso S, Kenis G, De Jongh R, et al. Negative immunoregulatory effects of antidepressants: inhibition of interferon-gamma and stimulation of interleukin-10 secretion. Neuropsychopharmacology. 1999;20:370–9.
57. Galecki P, Galecka E, Maes M, Chamielec M, Orzechowska A, Bobińska K, et al. The expression of genes encoding for COX-2, MPO, iNOS, and sPLA2-IIA in patients with recurrent depressive disorder. J Affect Disord. 2012;138:360–6.
58. Cattaneo A, Gennarelli M, Uher R, Breen G, Farmer A, Aitchison KJ, et al. Candidate genes expression profile associated with antidepressants response in the GENDEP study: differentiating between baseline 'predictors' and longitudinal 'targets'. Neuropsychopharmacology. 2013;38:377–85.
59. Miller AH, Maletic V, Raison CL. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. Biol Psychiatry. 2008;65:732–41.
60. Miller AH, Raison CL. Immune system contributions to the pathophysiology of depression. Focus. 2008;6:36–45.
61. Maes M, Fisar Z, Medina M, Scapagnini G, Nowak G, Berk M. New drug targets in depression: inflammatory, cell-mediated immune, oxidative and nitrosative stress, mitochondrial, antioxidant, and neuroprogressive pathways. And new drug candidates—Nrf2 activators and GSK-3 inhibitors. Inflammopharmacology. 2012;20: 127–50.
62. Eller T, Vasar V, Shlik J, Maron E. Pro-inflammatory cytokines and treatment response to escitalopram in major depressive disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32:445–50.
63. Rosenblat JD, Cha DS, Mansur RB, McIntyre RS. Inflamed moods: a review of the interactions between inflammation and mood disorders. Prog Neuropsychopharmacol Biol Psychiatry. 2014;53:23–34.
64. Motivala SJ, Sarfatti A, Olmos L, Irwin MR. Inflammatory markers and sleep disturbance in major depression. Psychosom Med. 2005;67:187–94.
65. Hannestad J, DellaGioia N, Bloch M. The effect of antidepressant medication treatment on serum levels of inflammatory cytokines: a meta-analysis. Neuropsychopharmacology. 2011;36:2452–9.
66. McNally L, Bhagwagar Z, Hannestad J. Inflammation, glutamate, and glia in depression: a literature review. CNS Spectr. 2008;13:501–10.
67. Moon H, Mizara A, McBride SR. Psoriasis and psycho-dermatology. Dermatol Ther (Heidelb). 2013;3:117–30.
68. Moller M, Du Preez JL, Viljoen F, Berk M, Emsley R, Harvey BH. Social isolation rearing induces immunological, neurochemical, mitochondrial and behavioural deficits in rats, and is reversed by clozapine or N-acetyl cysteine. Brain Behav Immun. 2012;18:156–67.
69. Persoons JH, Schornagel K, Breve J, Berkenbosch F, Kraal G. Acute stress affects cytokines and nitric oxide production by alveolar macrophages differently. Am J Respir Crit Care Med. 1995;152:619–24.
70. Nguyen KT, Deak T, Owens SM, Kohno T, Fleshner M, Watkins LR, et al. Exposure to acute stress induces brain interleukin-1beta protein in the rat. J Neurosci. 1998;18:2239–46.
71. Maier SF, Watkins LR. Intracerebroventricular interleukin-1 receptor antagonist blocks the enhancement of fear conditioning and interference with escape produced by inescapable shock. Brain Res. 1995;695:279–82.
72. Kubera M, Symbirtsev A, Basta-Kaim A, Borycz J, Roman A, Papp M, et al. Effect of chronic treatment with imipramine on interleukin 1 and interleukin 2 production by splenocytes obtained from rats subjected to a chronic mild stress model of depression. Pol J Pharmacol. 1996;48:503–6.
73. Zhou D, Kusnecov AW, Shurin MR, DePaoli M, Rabin BS. Exposure to physical and psychological stressors elevates plasma interleukin 6: relationship to the activation of hypothalamic-pituitary-adrenal axis. Endocrinology. 1993;133:2523–30.
74. Kubera M, Obuchowicz E, Goehler L, Brzeszcz J, Maes M. In animal models, psychosocial stress-induced (neuro)inflammation, apoptosis and reduced neurogenesis are associated to the onset of depression. Prog Neuropsychopharmacol Biol Psychiatry. 2011;35:744–59.
75. Alesci S, Martinez PE, Kelkar S, Ilias I, Ronsaville DS, Listwak SJ, et al. Major depression is associated with significant diurnal elevations in plasma interleukin-6 levels, a shift of its circadian rhythm,
and loss of physiological complexity in its secretion: clinical implications. J Clin Endocrinol Metab. 2005;90:2522–30.
76. Miller GE, Stetler CA, Carney RM, Freedland KE, Banks WA. Clinical depression and inflammatory risk markers for coronary heart disease. Am J Cardiol. 2002;90:1279–83.
77. Bouhuys AL, Flentge F, Oldehinkel AJ, van den Berg MD. Potential psychosocial mechanisms linking depression to immune function in elderly subjects. Psychiatry Res. 2004;127:237–45.
78. Musselman DL, Miller AH, Porter MR, Manatunga A, Gao F, Penna S, et al. Higher than normal plasma interleukin-6 concentrations in cancer patients with depression: preliminary findings. Am J Psychiatry. 2001;158:1252–7.
79. Kahl KG, Rudolf S, Stoeckelhuber BM, Dibbelt L, Gehl HB, Markhof K, et al. Bone mineral density, markers of bone turnover, and cytokines in young women with borderline personality disorder with and without comorbid major depressive disorder. Am J Psychiatry. 2005;162:168–74.
80. Tiemeier H, Hofman A, van Tuijl HR, Kiliaan AJ, Meijer J, Breteler MM. Inflammatory proteins and depression in the elderly. Epidemiology. 2003;14:103–7.
81. Schlatter J, Ortuño F, Cervera-Enguix S. Monocytic parameters in patients with dysthymia versus major depression. J Affect Disord. 2004;78:243–7.
82. Ford DE, Depression Erlinger TP. C-reactive protein in US adults. Arch Intern Med. 2004;164:1010–4.
83. Danner M, Kasl SV, Abramson JL, Vaccarino V. Association between depression and elevated C-reactive protein. Psychosom Med. 2003;65:347–56.
84. Maes M. Major depression and activation of the inflammatory response system. Adv Exp Med Biol. 1999;461:25–46.
85. Levine J, Barak Y, Chengappa KN, Rapoport A, Rebey M, Barak V. Cerebrospinal cytokine levels in patients with acute depression. Neuropsychobiology. 1999;40:171–6.

86. Lanquillon S, Krieg JC, Bening-Abu-Shach U, Vedder H. Cytokine production and treatment response in major depressive disorder. Neuropsychopharmacology. 2000;22:370–9.
87. Rajagopalan S, Brook R, Rubenfire M, Pitt E, Young E, Pitt B. Abnormal brachial artery flow-mediated vasodilation in young adults with major depression. Am J Cardiol. 2001;88:196–8.
88. Sluzewska A, Rybakowski JK, Laciak M, Mackiewicz A, Sobieska M, Wiktorowicz K. Interleukin-6 serum levels in depressed patients before and after treatment with fluoxetine. Ann NY Acad Sci. 1995;762:474–6.
89. Maes M, Bosmans E, De Jongh R, Kenis G, Vandoolaeghe E, Neels H. Increased serum IL-6 and IL-1 receptor antagonist concentrations in major depression and treatment resistant depression. Cytokine. 1997;9:853–8.
90. Mikova O, Yakimova R, Bosmans E, Kenis G, Maes M. Increased serum tumor necrosis factor alpha concentrations in major depression and multiple sclerosis. Eur Neuropsychopharmacol. 2001;11:203–8.
91. Sluzewska A, Sobieska M, Rybakowski JK. Changes in acute-phase proteins during lithium potentiation of antidepressants in refractory depression. Neuropsychobiology. 1997;35:123–7.
92. Tuglu C, Kara SH, Caliyurt O, Vardar E, Abay E. Increased serum tumor necrosis factor- α levels and treatment response in major depressive disorder. Psychopharmacology (Berl). 2003;170:429–33.
93. Hestad KA, Tønseth S, Støen CD, Ueland T, Aukrust P. Raised plasma levels of tumor necrosis factor alpha in patients with depression. J ECT. 2003;19:183–8.
94. Owen BM, Eccleston D, Ferrier IN, Young AH. Raised levels of plasma interleukin-1beta in major and postviral depression. Acta Psychiatr Scand. 2001;103:226–8.
95. Thomas AJ, Davis S, Morris C, Jackson E, Harrison R, O'Brien JT. Increase in interleukin-1β in late-life depression. Am J Psychiatry. 2005;162:175–7.
96. Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. Trends Immunol. 2006;27:24–31.
97. Bonaccorso S, Marino V, Biondi M, Grimaldi F, Ippoliti F, Maes M. Depression induced by treatment with interferon-alpha in patients affected by hepatitis C virus. J Affect Disord. 2002;72:237–41.
98. Lotrich FE. Major depression during interferon-α treatment: vulnerability and prevention. Dial Clin Neurosci. 2009;11:417–25.
99. Beretta L, Cossu M, Marchini M, Cappiello F, Artoni A, Motta G, et al. A polymorphism in the human serotonin 5-HT2A receptor gene may protect against systemic sclerosis by reducing platelet aggregation. Arthritis Res Ther. 2008;10:R103.
100. Wright CE, Strike PC, Brydon L, Steptoe A. Acute inflammation and negative mood: mediation by cytokine activation. Brain Behav Immun. 2005;19:345–50.
101. Schiepers OJ, Wichers MC, Maes M. Cytokines and major depression. Prog Neuropsychopharmacol Biol Psychiatry. 2005;29:201–17.
102. Dunn AJ, Swiergiel AH, de Beaurepaire R. Cytokines as mediators of depression: what can we learn from animal studies? Neurosci Biobehav Rev. 2005;29:891–909.
103. Capuron L, Neurauter G, Musselman DL, Lawson DH, Nemeroff CB, Fuchs D, et al. Interferon-alpha-induced changes in tryptophan metabolism Relationship to depression and paroxetine treatment. Biol Psychiatry. 2003;54:906–14.
104. Maes M, Leonard BE, Myint AM, Kubera M, Verkerk R. The new '5-HT' hypothesis of depression: cell-mediated immune activation induces indoleamine 2,3-dioxygenase, which leads to lower plasma tryptophan and an increased synthesis of detrimental tryptophan catabolites (TRYCATs), both of which contribute to the onset of depression. Prog Neuro-Psychopharmacol Biol Psychiatry. 2011;35: 702–21.
105. Wang J, Dunn AJ. Mouse interleukin-6 stimulates the HPA axis and increases brain tryptophan and serotonin metabolism. Neurochem Int. 1998;33:143–54.
106. Maes M, Kubera M, Obuchowiczwa E, Goehler L, Brzeszcz J. Depression's multiple comorbidities explained by (neuro)inflammatory and oxidative and nitrosative stress pathways. Neuro Endocrinol Lett. 2011;32:7–24.
107. Al'Abadie MS, Kent GG, Gawkrodger DJ. The relationship between stress and the onset and exacerbation of psoriasis and other skin conditions. Br J Dermatol. 1994;130: 199–203.
108. Devrimci-Ozguven H, Kundakci TN, Kumbasar H, Boyvat A. The depression, anxiety, life satisfaction and affective expression levels in psoriasis patients. J Eur Acad Dermatol Venereol. 2000;14:267–71.
109. Magin P, Adams J, Heading G, Pond D, Smith W. Experiences of appearance-related teasing and bullying in skin diseases and their psychological sequelae: results of a qualitative study. Scand J Caring Sci. 2008;22:430–6.
110. Fava GA, Perini GI, Santonastaso P, Fornasa CV. Life events and psychological distress in dermatologic disorders: psoriasis, chronic urticaria and fungal infections. Br J Med Psychol. 1980;53:277–82.
111. Gupta MA, Schork NJ, Gupta AK, Kirkby S, Ellis CN. Suicidal ideation in psoriasis. Int J Dermatol. 1993;32:188–90.
112. Hardy GE, Cotterill JA. A study of depression and obsessionality in dysmorphophobic and psoriatic patients. Br J Psychiatry. 1982;140:19–22.
113. Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, et al. A meta-analysis of cytokines in major depression. Biol Psychiatry. 2010;67:446–57.
114. Breuer K, Göldner FM, Jäger B, Werfel T, Schmid-Ott G. Relationship between chronic stress and CRP levels in women with psoriasis. J Dtsch Dermatol Ges. 2016;14:528–30.
115. Schmid-Ott G, Jaeger B, Boehm T, Langer K, Stephan M, Raap U, et al. Immunological effects of stress in psoriasis. Br J Dermatol. 2009;160: 782–5.
116. Brown RP, Kocsis JH, Caroff S, Amsterdam J, Winokur A, Stokes P, et al. Depressed mood and reality disturbance correlate with decreased nocturnal melatonin in depressed patients. Acta Psychiatr Scand. 1987;76:272–5.
117. Kartha LB, Chandrashekar L, Rajappa M, Menon V, Thappa DM, Ananthanarayanan PH. Serum melatonin levels in psoriasis and associated depressive symptoms. Clin Chem Lab Med. 2014;52:1–3.
118. Sandyk R, Pardeshi R. Mood-dependent fluctuations in the severity of tardive dyskinesia and psoriasis vulgaris in a patient with schizoaffective disorder: possible role of melatonin. Int J Neurosci. 1990;50:215–21.
119. Carrillo-Vico A, Lardone PJ, Alvarez-Sánchez N, Rodríguez-Rodríguez A, Guerrero JM. Melatonin: buffering the immune system. Int J Mol Sci. 2013;14:8638–83.
120. Esposito E, Cuzzocrea S. Anti-inflammatory activity of melatonin in central nervous system. Curr Neuropharmacol. 2010;8:228–42.
121. Mozzanica N, Tadini G, Radaelli A, Negri M, Pigatto P, Morelli M, et al. Plasma melatonin levels in psoriasis. Acta Derm Venereol. 1988;68:312–6.
122. Miles A, Philbrick D. Melatonin: perspectives in laboratory medicine and clinical research. Crit Rev Clin Lab Sci. 1987;25:231–53.

123. Ozler M, Simsek K, Ozkan C, Akgul EO, Topal T, Oter S, et al. Comparison of the effect of topical and systemic melatonin administration on delayed wound healing in rats that underwent pinealectomy. Scand J Clin Lab Invest. 2010;70:447–52.
124. Sandyk R, Pardeshi R. Mood-dependent fluctuations in the severity of tardive dyskinesia and psoriasis vulgaris in a patient with schizoaffective disorder: possible role of melatonin. Int J Neurosci. 1990;50:215–21.
125. Johnson R, Staiano-Coico L, Austin L, Cardinale I, Nabeya-Tsukifuji R, Krueger JG. PUVA treatment selectively induces a cell cycle block and subsequent apoptosis in human T-lymphocytes. Photochem Photobiol. 1996;63:566–71.
126. Laing TJ, Richardson BC, Toth MB, Smith EM, Marks RM. Ultraviolet light and 8-methoxypsoralen inhibit expression of endothelial adhesion molecules. J Rheumatol. 1995;22:2126–31.
127. Sethi G, Sodhi A. Role of p38 mitogen-activated protein kinase and caspases in UV-B-induced apoptosis of murine peritoneal macrophages. Photochem Photobiol. 2004;79:48–54.
128. Singh TP, Schön MP, Wallbrecht K, Michaelis K, Rinner B, Mayer G, et al. 8-Methoxypsoralen plus ultraviolet a therapy acts via inhibition of the IL-23/Th17 axis and induction of Foxp3+ regulatory T cells involving CTLA4 signaling in a psoriasis-like skin disorder. J Immunol. 2010;184:7257–67.
129. Diffey BL. Ultraviolet radiation physics and the skin. Phys Med Biol. 1980;25:405–26.
130. Kannan S, Heller MM, Lee ES, Koo JY. The role of tumor necrosis factor-α and other cytokines in depression: what dermatologists should know. J Dermatolog Treat. 2013;24:148–52.
131. Golpour M, Hosseini SH, Khademloo M, Ghasemi M, Ebadi A, Koohkan F, et al. Depression and anxiety disorders among patients with psoriasis: a hospitalbased case-control study. Dermatol Res Pract. 2012;2012:381905.
132. Dalgard FJ, Gieler U, Tomas-Aragones L, Lien L, Poot F, Jemec GB, et al. The psychological burden of skin diseases: a cross-sectional multicenter study among dermatological out-patients in 13 European countries. J Invest Dermatol. 2015;135:984–91.
133. Demirhan O, Demirbek B, Tunç E, Uslu IN, Çetiner S, Serin A. Identification of chromosome abnormalities in screening of a family with manic depression and psoriasis: predisposition to aneuploidy. Asian J Psychiatr. 2012;5:169–74.
134. Tohid H, Aleem D, Jackson C, Major Depression, Psoriasis. A Psychodermatological Phenomenon. Skin Pharmacol Physiol. 2016;29:220–30.
135. Pompili M, Innamorati M, Trovarelli S, et al. Suicide risk and psychiatric comorbidity in patients with psoriasis. J Int Med Res. 2016;44 1 Suppl:61–6.
136. Sbidian E. Suicide and psoriasis: no longer an association. Br J Dermatol. 2016;175:456–7.
137. Gooderham M, Gavino-Velasco J, Clifford C, MacPherson A, Krasnoshtein F, Papp K. A Review of Psoriasis, Therapies, and Suicide. J Cutan Med Surg. 2016;20:293–303.
138. Innamorati M, Quinto RM, Imperatori C, Lora V, Graceffa D, Fabbricatore M, et al. Health-related quality of life and its association with alexithymia and difficulties in emotion regulation in patients with psoriasis. Compr Psychiatry. 2016;70:200–8.
139. Drugs That Can Trigger Psoriasis Flares. Available from: http://www.webmd.com/skin-problems-and-treatments/psoriasis/drugs-worsen-psoriasis.
140. Gravani A, Gaitanis G, Zioga A, Bassukas ID. Synthetic antimalarial drugs and the triggering of psoriasis — do we need disease-specific guidelines for the management of patients with psoriasis at risk of malaria? Int J Dermatol. 2014;53:327–30.
141. Fry L, Baker BS. Triggering psoriasis: the role of infections and medications. Clin Dermatol. 2007;25:606–15.