Review article

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

Daniyal Aleem\textsuperscript{a}, Hassaan Tohid\textsuperscript{b,∗}

\textsuperscript{a} Center for Mind & Brain, Department of Neurology University of California Davis Fairfield, California, United States
\textsuperscript{b} Department of Neurology, University of California San Diego, California, United States

\textbf{A R T I C L E  I N F O}

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\textbf{A B S T R A C T}

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-\(\alpha\), interleukin 1 (IL-1), IL-2, IL-10, IL-22, IL-17, interferon-\(\gamma\), IL-1\(\beta\), 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.

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\textbf{C itocinas proinflamatorias, biomarcadores, genética y sistema inmunológico: un enfoque mecanicista de la depresión y la psoriasis}

\textbf{R E S U M E N}

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-18, la prostaglandina E2, la proteína C reactiva, la IL-6 y la IL-8, etc.— y algunos cambios genéticos.
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, which is a sub-branch of psychosomatic medicine. The effects of behavioral, social, and psychological factors on the bodily processes and their relationship with each other are studied in psychosomatic medicine. 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. 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. Similarly, psoriasis is a chronic, immune mediated inflammatory disease of skin that leads to red, itchy plaques (white/silver) on the skin. 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.

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. 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. 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 symptoms, in a study done in 2002, where psoriatic patients were found to have even higher depressive “scores” than non-psoriasis afflicted depressed patients. Topping it however, Gupta et al. 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. 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) 1b, 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. IL-6 and other cytokines are thought to influence maturation of T cells into Th17 cells, pulling neutrophils to specified location. IFN-γ and TNF-α levels may also be elevated from either Th1 or Th17 cells, and further amplify
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. IL-21, IL-17, and transforming growth factor β (TGF-β) are found in the people suffering from major depressive disorder. Specifically, increased levels of IP-10, or CXCL10, factors known to be involved in the localization of T cells, dendritic cells, and macrophages, were found in depressed patients, with antidepressants such as SSRIs lowering concentration, and increasing production of anti-inflammatory cytokines. Interestingly, changes in leukocyte mRNA expression, mRNA coding for cyclooxygenase-2, myeloperoxidase, inducible nitric oxide synthase and secretory phospholipase A2 type II A, have been observed in chronically depressed patients, with inflammatory gene expression lowering 8 weeks after treatment. 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. 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. This chronic inflammation independently has also been shown to be associated with the presence of depression and other psychological disorders. Remission of clinical depression through antidepressant treatment has shown normalization of inflammation related substances.

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). 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. 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. TNF-α has been thought to be linked to greater 5-HTT availability with TNF-α inhibition decreasing 5-HTT availability. 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. 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. 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.
Table 1 – Showing some relevant studies about the association of depression and psoriasis.

<table>
<thead>
<tr>
<th>Author/Publication year</th>
<th>Country</th>
<th>Study Design</th>
<th>Population</th>
<th>Sample Size</th>
<th>Diagnostic Criteria</th>
<th>Main Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Beelen et al. 2007</td>
<td>Netherlands</td>
<td>Review</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>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. Results suggest that Th17 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.</td>
</tr>
<tr>
<td>Zheng et al. 2007</td>
<td>USA</td>
<td>Review</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>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.</td>
</tr>
<tr>
<td>Lowes et al. 2008</td>
<td>USA</td>
<td>Longitudinal Study</td>
<td>Healthy volunteers skin (n=4), abdominoplasty normal skin (n=4), moderate to severe psoriasis patients skin (n=6), psoriasis patients (n=11)</td>
<td>12 skin samples, 11 patients</td>
<td>Unspecified</td>
<td>Calciptriol 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 diphonate 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 calciptriol monotherapy. However, the combination had a profound effect on, virtually, all T-cell subsets, beyond the effect of the monotherapies. 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.</td>
</tr>
<tr>
<td>Vissers et al. 2004</td>
<td>USA</td>
<td>Longitudinal Study</td>
<td>patients with chronic plaque psoriasis</td>
<td>7 psoriasis patients</td>
<td>Unspecified</td>
<td>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.</td>
</tr>
<tr>
<td>Urpe et al. 2005 USA</td>
<td>Review</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Farber et al. 1990 USA</td>
<td>Cross Sectional Study</td>
<td>Chronic plaque psoriasis patients in whom cutaneous nerve damage resulted in clearance of the disease at that site</td>
<td>2 patients</td>
<td>Unspecified</td>
<td>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.</td>
<td></td>
</tr>
<tr>
<td>Angiolillo et al. 1995 USA</td>
<td>Longitudinal Study</td>
<td>6-wk-old female BALB/c nu/nu mice and mouse cell cultures</td>
<td>4 mice and mouse cell cultures</td>
<td>Unspecified</td>
<td>Unspecified</td>
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existence a physiological relationship. 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. 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. 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. 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. Additionally, CRP and IL-6 measurements were observed to correlate to the onset of future depression in a 12-year study.

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. 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. Increased breakdown of serotonin may also be caused by the presence of inflammatory cytokines, and serotonin breakdown can lead to depressive symptoms. 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 melanocyte, anxiety, fatigue, and eventually depression. 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. Risk of developing psoriasis has also been shown to be significantly higher in depressed patients, corroborating this finding. Additionally, CRP has been present in depressed patients with levels at times showing a dose response with depressive morbidity 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.

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. 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. Decreased melatonin levels have been observed in a number of inflammatory conditions, with psoriasis included. 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. Treatment of depression can also return melatonin to healthy concentrations and decrease psoriasis symptomology. 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. Phototherapy can regulate melatonin levels, decrease psoriasis symptoms, and lessen depressive symptoms that further aggravate psoriasis. 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.

Aside from biomarkers, a study done in 2012 indicates the potential of a genetic connection between depression and psoriasis. Utilizing methods such as G-banding and cell cultivation, changes in chromosomes 8, 15, 21, 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)(2;4)(p25;p12), t(2;22)(p14;p13), t(19;Y), and dup(10)(q26) 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.

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. 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. Psoriasis is also associated with alexithymia and anxiety. 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.\textsuperscript{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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