Psoriasis is an inflammatory, immune-mediated disease that is frequently associated with psychological comorbidities such as depression. The stigma patients feel because of the appearance of their skin may contribute to the high psycho-social burden of psoriasis. However, there is emerging evidence that overlapping biological mechanisms are, to a substantial degree, responsible for the close interaction between psoriasis and depression. Increased proinflammatory mediators, such as C-reactive protein or interleukin-6, are present in both psoriasis and depression, indicating that inflammation may represent a pathophysiological link between the diseases. Anti-inflammatory biologic therapies treat the clinical manifestations of psoriasis, but might also play a significant role in reducing associated depressive symptoms in patients with psoriasis. Comparison between single studies focusing on the change in depressive symptoms in psoriasis is limited by inconsistency in the depression screening tools applied.

Key words: psoriasis; depression; psychological comorbidity; inflammation; pathophysiological link; depression screening tools.

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Psoriasis is a chronic inflammatory disease that leads to typical erythematous, scaly skin plaques. It affects nearly 2 million people in Germany (1) and is highly associated with psychological comorbidities, such as depression and anxiety disorders (2, 3). screenings of patients with psoriasis seeking help in dermatological clinics found prevalence rates for clinical depression of approximately 12–13% using International Classification of Diseases (ICD) codes (4–6). However, depending on the screening methodology, depressive symptoms are described as present in up to 28–55% of patients with psoriasis (6, 7). Anxiety disorders are prevalent in 7–48% of patients with psoriasis (5, 8). Given these high numbers of psychological comorbidities, the integrative management of patients with psoriasis in dermatological practice is essential (9–12). To this end, the establishment of an easy-to-use screening tool would be an important addition to routine clinical practice, ensuring the detection of affected patients, as these conditions are a major source of disability and may also hamper successful dermatological treatment (13, 14). Thus, the subject of the different screening tools will be discussed throughout this paper.

One possible explanation for the close association between psychological burden and psoriasis is the common stigmatizing attitude of society due to easily visible skin manifestations in affected patients. This hypothesis is supported by the fact that social stigmatization seems to be a strong predictor of depressive symptoms in patients with psoriasis (15). However, this relatively straightforward explanation may not be sufficient to account for all the observed effects.

Another hypothesis that is currently increasingly discussed suggests that immunological factors could be responsible for the association between depressive symptoms and inflammatory skin diseases, such as psoriasis. For years, depression has been attributed to reductions in monoaminergic neurotransmitters in the central nervous system (CNS), as monoamine agonists improve symptoms in a group of involved patients (16–18). However, it is now established that cytokine-mediated communication between the immune system and the brain plays a central role in the pathogenesis of depression (19–22). Studies have found increased serum levels of proinflammatory cytokines, such as tumour 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 who had depression without other inflammatory comorbidities (23–27) (Fig. 1). Conversely, there is a high prevalence of depressive symptoms in patients with chronic inflammatory diseases, such as rheumatoid arthritis or inflammatory bowel disease
In addition, patients on cytokine therapy treated with, for example, interferons report a high incidence of depression as unwanted side-effect (19, 20, 31). These clinical observations are supported by experimental data in healthy subjects who develop depressive symptoms following peripheral immune challenges induced by vaccination or bacterial endotoxin injection (32–35).

There are several theories about how elevated pro-inflammatory cytokines might influence the metabolism of neurotransmitters within the CNS. One theory assumes a hyperpermeable blood–brain barrier in patients with major depression that allows serum proinflammatory cytokines to enter the CNS (36). Once proinflammatory cytokines are present in the CNS, they are able to activate neuronal and non-neuronal cells, similar to their mode of action in the peripheral immune system (37). Another pathway discussed in the literature is the activation of cerebral vasculature endothelial cells leading to the secretion of cytokines inside the blood–brain barrier (27, 38). A third explanatory approach assumes that peripheral inflammatory signals can be transmitted to the CNS via the vagus nerve, as vagus nerve fibres have receptors that can bind serum proinflammatory cytokines (39).

As a consequence of this theoretical approach, peripheral low-grade inflammation is increasingly seen as a potential therapeutic target in depression. Different studies investigating the anti-depressive efficacy of anti-inflammatory treatments, such as non-steroidal anti-inflammatory drugs (NSAIDs) or cytokine blockers, have been performed, in some cases with promising results (20, 22, 40). Further studies assessing, amongst others, the anti-depressive effects of IL-6 inhibitors, are currently recruiting specifically depressed patients with elevated levels of CRP (41). An overview of anti-inflammatory agents and an assessment of their potential regarding anti-depressant treatment is available (42).

Mirroring the broadened concept of depression, psoriasis is no longer considered an isolated skin disease. Current understanding views psoriasis as a systemic inflammatory condition with documented proinflammatory reactions that go beyond the skin (43). The observation of peripheral inflammation both in psoriasis and in depression suggests that this may be one of the shared mechanisms of both diseases, underlying the high rates of psychological comorbidity and, especially, depression (for a review see, for example, 44 and 45).

Fig. 1. Psoriasis is a chronic inflammatory disease, frequently associated with depressive symptoms, which, on the one hand, are in part induced by the appearance of the skin and the resulting stigmatization felt by patients. However, on the other hand, there is emerging evidence that increased peripheral inflammatory responses are responsible for the induction and maintenance of depressive symptoms. In addition, psycho-social stress also affects immune responses. Future research is needed to unravel these functional interconnections among inflammatory responses, psoriasis and depressive symptoms. The insights obtained need to be considered in clinical practice.
**THE ROLE OF INFLAMMATION**

In light of the theories detailed above, it is relevant to take a closer look at the cytokines that play a role in both pathologies. The question, as to which serum proinflammatory cytokines show altered levels in patients with psoriasis, has been addressed in several reviews; see, for example (46–48). Dowlatshahi et al. (46) critically considered the inconsistency of methods resulting in a high heterogeneity of results. Nonetheless, the authors found sufficient evidence to state that levels of the proinflammatory cytokines IL-6 and TNF-α are consistently elevated in psoriasis, in addition to CRP, E-selectin and intercellular adhesion molecule 1 (ICAM-1). These findings are supported by a more recent meta-analysis by Bai et al. (47). However, 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 (49–51), an increased concentration of serum IL-17 may be expected. However, the data remains inconclusive, with some original studies showing elevated IL-17 levels (49), but both negative (46, 47), and positive (48) results in meta-analyses.

A quite comprehensive original study analysed 157 blood proteins in 266 patients with psoriasis (52). This study found significant correlations of pre-treatment PASI with IL-17C, IL-17A, and IL-6. Thus, there is some overlap with those cytokines elevated in depression (for a review see (45)). However, with only modest differences compared with healthy controls, these immune markers do not qualify as markers of disease severity in patients with psoriasis (46).

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 of depressive symptoms with systemic inflammation markers in patients with psoriasis. At least on the clinical level, depression is more common in patients with severe psoriasis, underlining the cytokine hypothesis. However, patients with mild psoriasis can also have relevant mental health problems (44, 45, 53). To the best of our knowledge, there is only one study to date that has investigated the correlation of depression in patients with psoriasis with serum inflammation markers: Pietrzak et al. (54) found serum concentrations of IL-18 to correlate with the severity of depressive symptoms in men with psoriasis (r=0.27). However, care is needed in interpreting correlations, and there may be additional variables influencing both psoriasis and depression. A possible candidate would be obesity, as this is a risk factor for incident psoriasis, aggravates existing psoriasis (55, 56), and is itself associated with systemic inflammation (57), as well as depression (58). In their model, Pietrzak et al. (54) did not control for body mass index (BMI) and, even though they did not find a significant correlation of BMI with depression in their sample, another study found BMI to at least to be associated with health-related quality of life (HR-QoL) in patients with psoriasis (10). Future studies looking into the inflammatory overlap of psoriasis and depression should thus control for obesity.

To follow up on the inflammation approach, it may be worthwhile studying psoriatic arthritis (PsA). While this subpopulation of patients with psoriasis may, in some cases, show milder skin symptoms (59), patients with PsA are characterized by additional physical disability and, on average, exhibit higher rates of comorbid depression (44, 45, 60). There is evidence of an increased inflammatory burden in patients with PsA compared with those with psoriasis without comorbid PsA, which is clinically also reflected in an increased cardiovascular comorbidity (61). This fits with the view that peripheral inflammatory processes represent a main linking mechanism between psoriasis and depression. More research on those 2 subpopulations of patients with psoriasis is needed in order to follow up on this idea.

The argument that the overlap of psoriasis and depression is associated with the systemic inflammation underlying both conditions would imply that, as psychological and psoriatic symptoms improve under therapy, so does the inflammatory burden. No study has addressed this directly so far. However, some studies have investigated the development of inflammatory markers under anti-psoriatic therapy. One marker that has been assessed repeatedly and was found to decrease in its levels over the course of treatment is CRP (respectively high-sensitive (hs) CRP) (62–64). While data on other biomarkers is more heterogeneous, again owing to a high heterogeneity of study protocols, there is some evidence for a reduction in the levels of several proinflammatory cytokines over the course of psoriasis treatment (52, 63–65). Kim et al. (52) 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. Amongst others, IL-6 was 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 (43, 66). In 2015, an initial study investigated in how far TNF-α inhibition or therapy with methotrexate may have positive effects on cardiovascular risk in patients with rheumatoid arthritis and PsA, respectively plaque psoriasis. Limited evidence suggests that these systemic therapies are associated with a decrease in cardiovascular risk (67). Two years later, Wu et al. (68) expanded evidence on this issue as they demonstrated 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-IL23, anti-IL18, anti-IL22, anti-IL23, and anti-ICAM-1) was associated with a lower incidence of cardiovascular events (69). These findings support the view that anti-psoriatic therapy reduces the inflammatory burden, which in turn may reduce cardiovascular risk.
anti-IL17) in severe psoriasis was associated with favourable modulation of coronary plaque indices, as measured by coronary computed tomography angiography (69). 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 (70).

While there is some evidence for the idea of psoriatic inflammation triggering depression, this association appears to be bi-directional (32). The skin manifestations of psoriasis often worsen with increasing psychological stress, and stressful life events have been shown to play a role in induction or exacerbation of psoriasis (45, 53, 71). This clinical observation is underpinned by experimental data indicating that stress and central nervous 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 proinflammatory cytokine profile, including IL-1, IL-6 and TNF-α (72).

**CHANGES IN PSYCHOLOGICAL SYMPTOMS UNDER ANTI-PSORIATIC THERAPY**

Clinical psoriasis studies investigating different therapeutic agents have shown improved courses of depression under anti-inflammatory therapies (73–77). However, data in this field are relatively scarce, as only a minority of the pivotal studies to date have used psychometric scales in their assessments of quality of life in general and depressive symptoms in particular. Studies employing the Dermatological Life Quality Index (DLQI) consistently showed that systemic therapy, especially with biologic agents, in general is superior to placebo in improving skin-related quality of life (78–80). These data suggest an improvement in psychological well-being under therapy; however, HR-QoL encompasses more than just symptom reduction, mobility and time spent on treatment. This is reflected by the fact that one-third of patients who screened positive for depression or anxiety were found to have inconspicuous scores on the DLQI, which illustrates the insufficiency of the DLQI as a sole screening tool (5).

In addition to the DLQI, some of the pivotal studies included the Short Form Health Survey-36 (SF-36), a generic instrument not specifically tailored for dermatological diseases (81), including subscales analysing physical as well as mental well-being, enabling comparison between distinct diseases. The SF-36 mental scores were found to be improved after treatment with ustekinumab (PHOENIX) (82) and brodalumab compared with placebo (phase-II study) (83) and secukinumab compared with fumaric acid esters (“PRIME” trial) (84). In addition, a 1-arm study also found improvements in the short version SF-12 after treatment with adalimumab (85).

One 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 (74), AMAGINE-1 (86) and VOYAGE (74, 87) 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 (85) and etanercept (14, 88–90).

Another well-known measure for the assessment of depressive symptoms is Beck’s Depression Inventory (BDI). This scale was employed in 2 older studies assessing the efficacy of etanercept (91, 92) and reported improved BDI scores over the course of treatment. However, this TNF-α antagonist is hardly prescribed anymore in plaque psoriasis.

Table I presents an overview of studies on biologic anti-psoriatic treatments that included psychological measures beyond the DLQI. In addition to the measures described above, some measures were employed only in single studies (91, 93).

So far, no meta-analysis has focussed on the question of an improvement in depressive symptoms under anti-inflammatory treatment exclusively in patients with psoriasis. However, studies employing different approaches have reported associations between improvement in psoriasis and amelioration of psychological symptoms under biologic therapies (74, 91, 93). In addition, anti-inflammatory treatment has demonstrated an anti-depressant effect in patients with inflammatory diseases (76, 77).

**FROM BENCH TO BEDSIDE**

Current understanding of psoriasis has evolved from a mere skin condition to a multifactorial systemic disease. In parallel, there is increasing evidence suggesting an association between depression and inflammation. Proinflammatory cytokines, such as CRP and IL-6, are elevated in both psoriasis and depression, indicating that the inflammatory process may represent a pathophysiological link between these diseases.

Fittingly, large epidemiological studies confirm that the risk of comorbid depression is significantly higher in individuals with psoriasis compared with those without (94, 95). In consideration of the high rate of depression and other psychological disorders, such as anxiety in patients with psoriasis, routine screening for psychological comorbidities is essential in dermatological practice to manage these patients interdisciplinarily.
involving mental healthcare professionals whenever necessary (9–12). This is especially relevant, as some evidence suggests that baseline depression and persistent depression during treatment could be indicative of a less favourable treatment course (14, 90). Furthermore, when making a therapy decision, the dermatologist has to take into account that caution is required prior to prescribing any anti-psoriatic treatment. In order to avoid a less favourable treatment course (14, 90), if patients answer “yes” to both questions, referral to the primary care physician, or preferably to a psychiatrist or psychotherapist, is indicated in order to confirm the presence of depression. Several studies that have assessed the efficacy of anti-psoriatic treatments for psoriasis disorders and mental health problems in general is not yet well established in Europe (97).

One reason impeding the screening of patients with psoriasis for comorbid psychological disorders might be that referral to mental healthcare is often difficult and associated with long waiting times; hence some dermatologists may not find out that their patients are in need of psychological care.

Another factor explaining the lack of screening in the clinical routine may be that there is no established screening tool for the assessment of psychological co-morbidity that is consistently recommended. A tool for the dermatological practice that is at least recommended by the German National Conference on Healthcare in Psoriasis is Whooley’s “Two-Questions Test” (Table II) (12, 98, 99). If patients answer “yes” to both questions, referral to the primary care physician, or preferably to a psychiatrist or psychotherapist, is indicated in order to clinically detect formal diagnostic criteria. However, to the best of our knowledge, this screening tool has not been used in any of the treatment studies.

Several studies that have assessed the efficacy of systemic treatments for psoriasis could show an improvement in psychological symptoms over the course of treatment (76, 77). However, the number of studies that have addressed this question is small. In part, this may be attributed to the fact that most pivotal trials testing new anti-psoriatic treatments comparing the efficacy of different molecules have not yet used psychological evaluation tools or have not yet used psychological evaluation tools in their pivotal trials.

Table I. Overview of psychological assessments used in studies on anti-psoriatic treatments employing tumour necrosis factor-alpha, interleukin-(12)/23 and -17 inhibitors

| Measure                  | Study Medication | Design                      | Number of patients | Outcome                              | Confirmation of hypothesis?* |
|--------------------------|------------------|-----------------------------|--------------------|--------------------------------------|-----------------------------|
| **Tumour necrosis factor-alpha inhibitors** |                  |                             |                    |                                      |                             |
| HADS                     | Adalimumab       | One arm, observational      | 143                | HADS at week 4 and 16 and 6 months   | Yes                         |
|                          | Etanercept       | Two groups (different etanercept regimens), open-label | 711, 2 groups (1:1): continuous and interrupted etanercept | HADS at week 54 | Yes |
|                          | Etanercept       | Two groups (different etanercept regimens), randomized, double-blind | 752, 2 groups (1:1): etanercept once or twice weekly | HADS at week 12 and 24 | Yes |
| BDI                      | Etanercept       | One arm, observational      | 85                 | HADS at 1, 3 and 6 months            | Yes                         |
|                          | Etanercept       | Two groups (different etanercept regimens), open-label | 133                | HADS at 1, 3 and 6 months            | Yes                         |
| Hamilton rating scale for depression | Etanercept | RCT, placebo controlled   | 618, 2 groups (1:1): etanercept or placebo | BDI at week 12 | Yes |
| SF-36 mental subscore    | Adalimumab       | RCT, placebo controlled    | 96, 2 groups (1:1): adalimumab or placebo | SF-36 at week 12 | Not assessed |
| SF-12                    | Adalimumab       | Real-world, observational   | 143                | SF-12 at week 4 and 16 and 6 months | Yes (No for week 4 vs baseline) |
| ZDS                      | Adalimumab       | RCT, placebo controlled    | 96, 2 groups (1:1): adalimumab or placebo | ZDS at week 12 | Yes |
| **Interleukin-(12)/23 inhibitors** |                  |                             |                    |                                      |                             |
| HADS                     | Ustekinumab      | RCT, placebo controlled    | 1,230, 3 groups (1:1:1): ustekinumab (2 dosages), placebo | HADS at week 12 | Yes |
|                          | Guselkumab       | RCT, placebo controlled    | 992, 3 groups (2:1:1): guselkumab, adalimumab or placebo | HADS at week 16 and week 24 | Yes |
| SF-36 mental subscore    | Ustekinumab      | RCT, placebo controlled    | 766, 3 groups (1:1:1): ustekinumab (2 dosages) or placebo | SF-36 at week 12 | Yes |
| **Interleukin-17 inhibitors** |                  |                             |                    |                                      |                             |
| HADS                     | Brodalumab       | RCT, placebo controlled    | 633, 3 groups (1:1:1): brodalumab (2 dosages), placebo | HADS at week 12 | Yes |
| SF-36 mental subscore    | Brodalumab       | RCT, placebo controlled    | 198, 5 groups (1:1:1:1:1): brodalumab (4 dosages) or placebo | SF-36 at week 12 | Yes (No for the smallest dosage) |
|                          | Secukinumab      | RCT, compared with fumaric acid ester | 200, 2 groups (1:1): secukinumab or fumaric acid ester | SF-36 at week 24 | Yes |

*In placebo-controlled randomized controlled trials (RCTs): improvement in psychological symptoms under therapy > placebo; in studies without placebo control: improvement in psychological symptoms under therapy.

BDI: Beck’s Depression Inventory; SF: Short Form Health Survey; HADS: Hospital Anxiety and Depression Scale; ZDS: Zung Self-Rating Depression Scale.

Table II. Whooley’s “Two-Questions Test”

1. “Have you frequently felt dejected, sad, glum or hopeless during the past month?”
2. “Have you taken significantly less pleasure and joy in things, which you otherwise enjoy doing, over the past month?”

Adopted from: (12, 98, 99)
compounds generally exclude patients with depression and suicidal ideation behaviour. Real-word, longitudinal observational studies investigating the improvement in psychological symptoms under anti-psoriatic treatment might be better suited to also making a statement on patients with clinically significant depression; however, the database is also meagre.

A question that is difficult to answer in the overall context is in how far improved depression is a direct effect of the anti-inflammatory treatment, or rather an indirect effect of the improved skin condition that leads to a better psychological status (45). To approach this question, it is worthwhile to examine how improvements in skin symptoms and psychological symptoms relate. As a major burden on the psyche of patients with psoriasis is the stigma and possible social isolation connected with the disease, a close association of objective and subjective symptom measures appears intuitive. However, results are highly heterogeneous, and correlations are seldom more than moderate, suggesting that much of the variance in psychological symptoms cannot be explained by the presence of, or changes in, skin symptoms alone.

There are several possible explanations for a relatively weak connection of objective and subjective measures. In contrast to intuition, it may not be as easy as to “cure the skin symptoms and the psyche will follow.” It could rather be possible that the anti-psoriatic and thus anti-inflammatory medication exerts a direct effect on the psyche as it reduces inflammation associated with depression. On the other hand, it is also possible that the reasons for depressive behaviour and social isolation go beyond what can be cured by anti-psoriatic treatment: even though skin symptoms recede, it may be difficult to let go of habits that have developed during a lifetime of psoriasis burden (100). Early initiation of an effective anti-psoriatic therapy is of high importance in order to avoid cumulative life course impairment for affected children and adolescents (53, 101).

In conclusion, this review examined the literature on the interaction of psoriasis and depression, and the influence of anti-psoriatic treatment on depressive symptoms. Depression is a frequent comorbidity of psoriasis. Previously, stigmatizing experiences were primarily believed to be responsible for this association. However, currently there is accumulating evidence that overlapping biological mechanisms contribute to the close connection of psoriasis and depression. Elevated levels of proinflammatory cytokines are present in psoriasis and depression, indicating that inflammation may represent a pathophysiological link between both diseases. As the 2 are closely related, it is difficult to differentiate whether improvement in depression is the result of a direct anti-inflammatory effect of the biologic, or rather an indirect effect of improved skin leading to amelioration of psychological symptoms. Several studies confirm improvements in both skin and psychological symptoms under biologic therapy; however, these improvements are often not as closely related as one would expect if the reduction in depressive symptoms was a direct effect of the improvement in skin symptoms. Data from meta-analyses demonstrated an anti-depressant effect of anti-cytokine treatments even if the somatic disease did not respond to treatment, which makes a direct effect of the biologic more likely. Furthermore, clinical trials indicated anti-depressant treatment effects of anti-inflammatory agents, such as TNF-α antagonists in the treatment of depression, and new directions in targeting inflammatory mechanisms, e.g. with IL-6 inhibitors, are underway.

In order to optimize comparisons of changes in psychological symptoms under anti-psoriatic therapy across different treatment types and studies, a consensus needs to be reached on specific depression screening tools. Likewise, screening for comorbid depression should be standardized and implemented on a regular basis in dermatological practice in order to alleviate the associated psychological burden.

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