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# The impact of antipsoriatic treatment on serum pro-BDNF, BDNF levels, depression, anxiety scores, and quality of life

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## Abstract

Depression is a comorbidity of psoriasis. Suppression of neurotrophins has been proposed to cause depression. Peripheral brain-derived neurotrophic factor (BDNF) and its precursor, pro-BDNF have been shown to be altered in depression. To compare serum pro-BDNF and BDNF levels, depression, anxiety, and quality of life (QoL) in psoriasis patients, diseased, and healthy controls, to assess impact of 12-week antipsoriatic treatment on abovementioned markers. At baseline, all groups completed Beck Depression Inventory (BDI), Spielberger State-Trait Anxiety Inventory-II (STAI-II) and DLQI; serum BDNF, proBDNF levels were measured. These were repeated after 3-months of treatment in psoriasis patients. Depression and anxiety were significantly higher, QoL was poorer in psoriasis. ProBDNF and proBDNF/BDNF ratios were not different among groups at baseline but significantly decreased after treatment in psoriasis. Depression and QoL improved significantly, BDNF and anxiety scores did not change. Altered pro-BDNF and proBDNF/BDNF ratios may have a role in depression pathogenesis in psoriasis. Antipsoriatic treatment causes improvement in depression, QoL, and reduction of proBDNF and proBDNF/BDNF ratios. Effective disease control may reverse dysregulated neurotrophin pathways and its consequences like depression.

**KEYWORDS**
anxiety, BDNF, depression, proBDNF, psoriasis, quality of life

## 1 | INTRODUCTION

Depression is a common psychiatric disorder with a lifetime prevalence of 6.1% to 9.5%.[1] It is one of the major comorbidities of psoriasis with a prevalence ranging between 10% and 62%.[2-4] Being one of the most important risk factors for suicide attempts, World Health Organization (WHO) estimates depression to be the largest leading cause ended up to death worldwide by 2030.[1] Various mechanisms like dysregulation of neurotransmitter systems, reduced levels of brain-derived neurotrophic factor (BDNF), hyperactivity of the hypothalamic pituitary adrenal (HPA) axis, and inflammatory cytokines or endogenous metabolites are being proposed to be involved in the etiology of depression.[5-7] Inflammatory cytokines, IL-$1_{\beta}$, IL-6, and TNF-α, which have important roles in pathogenesis of both depression and psoriasis are suggested to influence depression by supressing brain-derived neurostimulatory factor (BDNF) expression.[7-9] BDNF, also known as mature-BDNF, is one of the most widely expressed neurotrophins and is a key regulator of neuronal differentiation, repair, structure, and function. Decreased levels of hippocampal BDNF in stress-induced depressive conditions, upregulation of its expression following antidepressant therapy have been shown. Serum BDNF levels have been used as a biomarker for depression and to assess

**Abbreviations:** BDI, beck depression inventory; BDNF, brain-derived neurotrophic factor; DLQI, dermatology life quality index; PASI, psoriasis area and severity index; pro-BDNF, precursor for brain-derived neurostimulatory factor; QoL, quality of life; STAI-II, Spielberger stait-trait anxiety inventory-II.

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treatment response in various studies.[10,11] BDNF is synthesized from its precursor pro-BDNF which has been shown to exert opposing functions such as promotion of neuronal death.[12] A balance between pro-BDNF/mature BDNF levels has beeen claimed to have critical role in regulation of neural function. Taken together, investigating pro-BDNF and BDNF levels, as potential biomarkers of depression in psoriasis patients may be an intriguing topic of research, especially as such data is surprisingly sparse.

We hypothesized an imbalance between pro-BDNF and BDNF through chronic psoriatic inflammation to be a possible cause of increased depression risk in psoriasis and aimed primarily to investigate serum pro-BDNF and BDNF levels of psoriatic, diseased, and healthy controls. Secondary objectives were:

1. To assess the correlation of pro-BDNF and BDNF with disease severity and subjective measures of depression, anxiety, and quality of life (QoL).
2. To investigate the impact of 12-week antipsoriatic treatment on abovementioned markers.
3. To analyze the correlation between clinical improvement and aforementioned parameters.

## 2 | METHODS

### 2.1 | Study design and patients

We designed a prospective study in Marmara University Hospital, Department of Dermatology between March 2013 and September 2014. All participants provided written informed consent and the study was conducted in accordance with Declaration of Helsinki principles.

Study population included 31 psoriasis patients requiring systemic treatment, 31 control patients (acne, vitiligo, and other dermatologic diseases), and 31 healthy controls aged 18 to 65 years. Diagnosis and Psoriasis Area and Severity Index (PASI) assessments were made by the dermatologist. All participants had body mass index calculations. Subjects were excluded from the study if they had either current or past depression, any other neurological/psychiatric disorder, substance abuse, or use of psychotropic drugs. Psoriasis patients receiving any systemic antipsoriatic treatment or phototherapy within last 3 months were also exluded.

Data on sociodemographic and medical characteristics and comorbidities of psoriasis patients were collected.

### 2.2 | Treatment

Based on general health, physical examination findings and laboratory tests, most appropriate treatment was planned for psoriasis patients, as a part of routine daily practice. Treatment modalities included phototherapy, acitretin (0.3-0.5 mg/kg/day), methotrexate (10-25 mg/week with 10 mg/week folic acid supplementation), or cyclosporine (3-5 mg/kg/day). As preliminary data shows anti-TNF treatment to decrease BDNF levels, patients using biologics were excluded.[13]

Screening, management, and laboratory monitorization were performed according to guidelines for psoriasis treatment. Disease severity and treatment response were assessed by PASI at baseline and after 3-months treatment.

### 2.3 | Laboratory procedures

Five microliters fasting venous blood was collected from all participants at baseline. Additional blood samples were obtained from psoriasis patients following 3-months treatment. Serum samples were stored at −80°C until use. Serum levels of proBDNF and BDNF were measured by using the human proBDNF ELISA Kit (R&D Systems human Pro-BDNF) and the human BDNF ELISA Kit (R&D Systems Quantikine ELISA Human BDNF Immunoassay) according to manufacturer's instructions.[14] The analyst was blinded to the diagnostic status of participants when performing ELISA.

### 2.4 | Subjective scales

Depression, anxiety, and QoL were evaluated with relevant scales all of which have been validated for Turkish population.[15-18] Depressive symptoms were assessed using Beck Depression Inventory (BDI) with 21 items to evaluate hopelessness, guilty feelings, worthlessness, punishment feelings, self-dislike, suicidal thoughts as well as physical symptoms such as fatigue, weight loss, change in appetite and sleep, and lack of interest in sex. BDI scores range between 0 and 63, score above 19 indicating moderate-severe depression.[19]

Anxiety was assessed through Trait Anxiety Inventory (STAI-II) with 20 statements[20] and a total score of 20 to 80, higher scores indicating high anxiety levels.

QoL was assessed by Dermatology Life Quality Index (DLQI) questionnaire[21] which comprises 10 questions with six domains, including symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment difficulties. DLQI score varies from 0 to 30 with higher scores indicating greater impact on QoL.

### 2.5 | Statistical analysis

*SPSS* (*Statistical Package for Social Sciences*) *v17.0* was used to analyze data. Demographic data and general characteristics of psoriasis patients were analyzed by descriptive statistics. Chi-square test was used for categorical variables. For quantitative variables, independent samples *t*-test was used to compare two samples, ANOVA test was used to compare three samples. Appropriate test was selected considering normal distribution of data, homogenity of variance and sample size. Paired samples *t*-test was used to compare related samples. *P* value of <.05 was considered significant. Pearson correlation test was performed to analyze correlation between variables.

## 3 | RESULTS

### 3.1 | Patient and disease characteristics

Study group consisted of 31 psoriasis patients; 10 females and 21 males, aged 18 to 60, 31 diseased controls; acne ($n$ = 9), vitiligo ($n$ = 8), patients with other skin diseases ($n$ = 14) aged 23 to 65 and 31 age and sex-matched healthy controls.

Mean age of psoriasis patients, diseased and healthy controls were 36.8 (±11.6), 33.9 (±16.0), and 35.7 (±11.4), respectively. There was no significant difference in terms of age, sex, or marital status between groups.

Previous treatments of psoriatics included topical corticosteroids (95.9%), calcipotriol (59.2%), phototherapy (22.4%), methotrexate (14.3%), acitretin (14.3%), cyclosporine (8.2%), and biologics (12.2%). Disease characteristics are shown in Table 1.

### 3.2 | Baseline BDI, STAI-II, DLQI scores and serum Pro-BDNF, BDNF levels

Mean BDI scores of psoriasis, diseased, and healthy groups were 15.55, 11.87, and 8.9, respectively, with a significant difference between groups ($P$ = .026), particularly between psoriasis patients and healthy controls ($P$ = .005; Table 2). Females and especially females with psoriasis had significantly higher BDI scores compared to males (all subjects $P$ = .027 psoriasis patients $P$ = .029).

STAI-II scores were also significantly different between groups ($P$ = .008), particularly between psoriasis patients and healthy controls ($P$ = .010; Table 2).

At baseline, psoriasis patients had significantly higher DLQI scores compared to diseased controls (12.81 vs 5.39 $P$ = .013; Table 2). DLQI scores had a relation to disease severity with higher DLQI scores in severe (17.1) as compared to mild psoriasis (10.0; $P$ = .002).

**TABLE 1** Disease characteristics of psoriasis patients

| | |
|---|---|
| Disease duration (years) Mean ± SD (min-max) | 12.7 ± 7.9 (0-28) |
| PASI (n = 31) Mean ± SD (min-max) | 10.04 ± 6.5 (2.1-28) |
| Clinical variant | |
| Generalized plaque | 76.7% |
| Localized | 20.0% |
| Guttate | 3.3% |
| Arthritis | 10.0% |
| Comorbidities | |
| Obesity | 25.8% |
| Diabetes | 10.0% |
| Cardiovascular disease | 6.7% |
| Other | 26.7% |
| Body mass index (kg/m$^2$; mean ± SD) | 27.8 ± 6.4 |

Abbreviation: PASI, baseline PASI of patients; SD: Standart deviation.

Serum levels of proBDNF at baseline were 6106.5, 6660.9, and 4747.9 pg/mL for psoriasis, diseased, and healthy controls, respectively, with no significant difference among groups. Likewise, basal BDNF levels were comparable, 32 451.5, 35 291.1, and 32 887.6 pg/ml, respectively (Table 2).

### 3.3 | Impact of treatment on measures

Psoriasis patients were treated with acitretin (41.9%), phototherapy (32.3%), methotrexate (16.1%), and cyclosporine (9.7%). After 12-weeks treatment, mean PASI decreased from 10.04 to 2.94 ($P$ = .001; Table 3). At week 12, PASI 50, PASI 75, and PASI 90 responses were achieved in 71%, 48.4%, and 22.6% of patients, respectively.

After treatment, mean BDI and DLQI scores of psoriasis patients decreased from 15.55 to 13.06 ($P$ = .043) and 12.81 to 6.19 ($P$ = .001), respectively. However, no significant change could be detected in trait anxiety scores.

Although no significant change in BDNF levels was found after therapy ($P$ = .81), mean proBDNF levels decreased significantly from 6106.50 to 2190.58 after treatment ($P$ = .001). Likewise proBDNF/BDNF ratio changed significantly following treatment ($P$ = .001).

We further analyzed a subgroup of psoriasis patients with a depression score of >19, indicating moderate to severe depression, for change of these parameters through treatment (n = 11). Unsurprisingly, psoriasis patients with depression had a significant decrease in proBDNF levels following treatment (from 5161.3 to 1077.9, $P$ = .026). BDNF levels also tended to improve without any statistically significant change (from 8888.7 to 10 504.6, $P$ = .18).

### 3.4 | Correlations between parameters

As expected, a statistically significant but modest correlation was observed between PASI improvement and DLQI scores ($r$ = .471, $P \leq .009$). Likewise, improvement in BDI was found to have a significant correlation with DLQI ($r$ = .576, $P \leq .001$) and STAI-II scores ($r$ = .629, $P \leq .000$). A weak statistically significant correlation was also seen between improvement in scores of STAI-II and DLQI ($r$ = .430, $P \leq .018$).

## 4 | DISCUSSION

We have investigated serum BDNF and proBDNF levels and their relation to disease severity, subjective measures of depression, anxiety, QoL, and treatment response. We have found psoriasis patients to have higher depression and anxiety scores as well as poorer QoL compared to controls. In addition, significant decreases in PASI, proBDNF levels, proBDNF/BDNF ratio, BDI, and DLQI scores were detected following treatment.

Higher BDI scores in psoriasis patients in our study supports well-known relation between psoriasis and depression.[4,22,23] Correlation

**TABLE 2** Comparison of measures among study groups at baseline

| Scale/test | Psoriasis patients (n = 31) | Control patients (n = 31) | Healthy controls (n = 31) | *P* value |
|---|---|---|---|---|
| $BDI_1$ (Mean ± SD) | 15.55 ± 11.97 | 11.87 ± 8.99 | 8.90 ± 6.88 | **.026*** |
| $DLQI_1$ (Mean ± SD) | 12.81 ± 7.7 | 5.39 ± 4.89 | | **.013*** |
| STAI-$II_1$ (Mean ± SD) | 47.87 ± 10.6 | 45.97 ± 9.07 | 40.77 ± 7.37 | **.008*** |
| proBDNF$_1$ (pg/ml) (Mean ± SD) | 6106.50 ± 4776.97 | 6660.97 ± 6096.72 | 4747.99 ± 4199.75 | .318 |
| $BDNF_1$ (pg/ml) (Mean ± SD) | 32 451.52 ± 9949.70 | 35 291.16 ± 25 089.72 | 32 887.67 ± 8848.81 | .764 |
| proBDNF/BDNF ratio (Mean ± SD) | 0.2025 ± 0.16 | 0.2662 ± 0.36 | 0.1638 ± 0.16 | .260 |

*Note:* ANOVA is used to compare $BDI_1$ and STAI-$II_1$ scores, $BDNF_1$ and proBDNF$_1$ levels and proBDNF/BDNF ratio. Student *t* test is used to compare $DLQI_1$ scores.
Abbreviations: $BDI_1$, beck depression inventory baseline score; $BDNF_1$, BDNF levels at baseline; $DLQI_1$, dermatology life quality index baseline score; proBDNF$_1$, proBrain-derived neurotrophic factor at baseline; STAI-$II_1$, state-trait anxiety inventory II baseline score.
*$P < .05$ was considered statistically significant (in bold font).

**TABLE 3** Impact of treatment on measures

| Test/scale | Before treatment (Mean) | After treatment (Mean) | *T* value | *P* value |
|---|---|---|---|---|
| PASI | 10.04 | 2.94 | 5.515 | **.001*** |
| BDI | 15.55 | 13.06 | 2.117 | **.043*** |
| DLQI | 12.81 | 6.19 | 4.273 | **.001*** |
| STAI-II | 47.97 | 46.74 | 0.649 | .521 |
| proBDNF (pg/ml) | 6106.50 | 2190.58 | 5.241 | **.001*** |
| BDNF (pg/ml) | 32 451.52 | 30 150.60 | 0.958 | .346 |
| proBDNF/BDNF ratio | 0.2025 | 0.0866 | 5.245 | **.001*** |

*Note:* Paired samples *t*-test was used to compare pretreatment and posttreatment values.
Abbreviation: BDI, beck depression inventory; BDNF, brain-derived neurotrophic factor; DLQI, dermatology life quality index; PASI, psoriasis area and severity index; STAI-II, state-trait anxiety inventory II.
*$P < .05$ was considered statistically significant (in bold font).

between BDI and DLQI scores in our patients points out the impact of depression on poor QoL. In line with literature data demonstrating higher depression rates in female patients, our female psoriasis patients had significantly higher BDI scores.[24] Hence, management of psoriasis may include measures of additional support in females. Following treatment, mean BDI score in psoriasis patients decreased significantly. Consistent with our results, topical and systemic antipsoriatic treatments including etanercept, adalimumab, and ustekinumab all have been shown to improve depression scores.[25-28] Whether this improvement is a consequence of suppression of inflammatory mediators triggering pathways involved in depression pathogenesis or a decrease in psychosocial burden of psoriasis through disease control is a topic of interest.

Consistent with literature, STAI-II scores of our psoriasis patients were found to be significantly higher indicating increased anxiety risk. Previously, Zeljko-Penavić et al and Golpour et al have investigated anxiety in psoriasis using STAI and reported significantly higher scores in psoriasis patients.[29,30] In line with our results, these authors also found a correlation between STAI-II scores and BDI and DLQI scores. These findings point out that increased likelihood of depression and anxiety causes a poorer QoL in psoriasis or vice versa. One of the interesting findings of our study was lack of improvement in anxiety after treatment. Similar to our findings, Kabat-Zinn et al[31] were unable to see any change in STAI scores of psoriasis patients after phototherapy. Why does anxiety persist in spite of a significant clinical improvement, depression, and QoL? Although we have no straightforward explanation, past experiences of patients with a chronic, unstable disease, development of unresponsiveness to available treatments, may have caused trait anxiety. Another explanation may be the lack of assessment of state anxiety, which is more sensitive to short-term changes.

We have also found greater impact of psoriasis on QoL compared to diseased controls. Mean DLQI scores were significantly higher in severe cases (PASI > 10) and a statistically significant correlation was observed between PASI and DLQI scores. Although various studies revealed impaired QoL in vitiligo, acne, and psoriasis, detrimental

effect was found to be more prominent in psoriasis group in our study. Nevertheless, these results should be interpreted cautiously as DLQI is not a psoriasis-specific instrument and our psoriasis group had moderate-severe disease, not representing full spectrum of disease.[32,33] As expected, DLQI scores of psoriasis patients decreased significantly after treatment and showed a statistically significant correlation with PASI improvement. This finding also underscores the importance of effective disease control as active psoriasis per se is a major determinant of QoL.

Since inflammatory cytokines TNF-alpha and IL-1 beta suppress BDNF and low levels of BDNF is proposed to have a role in depression pathogenesis, we were expecting to find lower BDNF levels in psoriasis and a possible improvement following treatment.[34] However, no difference was found in baseline proBDNF and BDNF levels of the groups. Furthermore, despite effective disease control with PASI 75 response in nearly half of patients and significant reduction in depression scores, serum BDNF levels remained stable following treatment. This finding cannot be explained by the lack of anti-TNF agent use because the significant decrease in PASI and BDI scores indicates that conventional antipsoriatic agents have provided adequate anti-inflammatory effects. The stability of serum BDNF levels can be interpreted as a Type II error due to our small sample size or lack of sensitivity of serum BDNF levels as a marker for depression. Few studies have addressed serum BDNF levels in various skin disorders including vitiligo, atopic dermatitis, chronic spontaneous urticaria, and psoriasis with inconsistent results.[35-41] Among these, Brunoni et al reported decreased BDNF plasma levels in 94 psoriasis patients[35] and Sjahrir et al demonstrated a negative correlation between serum BDNF levels and severity of psoriasis,[36] whereas Raap et al and Narbutt et al, similar to our data, could not find any difference in serum BNDF levels of psoriasis patients.[37,41] These findings suggest that these neurotrophins may not be reliable and consistent biomarkers of depression. Recent studies have provided evidence on nonneuronal functions of BDNF and other neurotrophins in normal skin physiology such as development of sensory nervous system, function of cutaneous mechanoreceptors and hair cycle-dependent changes.[42] In addition, follicular keratinocytes, fibroblasts, T-cells, and platelets have been shown to express BDNF which have been proposed to have a role in neuroinflammation and stress response.[43] Taken together, despite the negative findings of our study, both peripheral and lesional BDNF should be studied further as it may bear a potential link to stress, psoriasis exacerbation, inflammation and depression.

A remarkable finding of our study was the significant reduction in serum proBDNF levels and proBDNF/BDNF ratio after treatment. Since higher serum proBDNF levels have been demonstrated in major depression, proBDNF may be one of the molecules mediating depression in psoriasis patients. As a balance between proBDNF and BDNF is claimed to be important for mood regulation and neuronal function, assessing this ratio may be more sensitive and informative.[44] In fact, proBDNF/BDNF ratio has been shown to be a highly reliable biomarker of biological stress in fish with sensitivity of 100%, specificity of 87%, positive predictive value of 88% and negative predictive value of 100%.[45] Moreover, Jiang et al[46] have shown that the BDNF/proBDNF ratio is significantly lower in patients with major depressive disorder compared to controls and significantly increased after antidepressant treatment, suggesting that the BDNF/proBDNF ratio is a biomarker of depression.

Our study has several limitations. First, depression and anxiety were not assessed by psychiatric examination, and the state anxiety inventory was not performed. Since psychiatric examination is time-consuming, costly and difficult to access, subjective scales had been widely used in research, as in our study. Second, psoriasis group was small and heterogeneous in terms of disease type, comorbidities and treatments which may explain our negative results of serum BDNF. Finally, markers of inflammation were not assessed making a conclusion on the relation between inflammation and BDNF impossible. Nonetheless, this study is first in evaluating both proBDNF and BDNF in psoriasis patients, utilizing PASI and subjective measures to make clinical correlations and assessing treatment effect. Its' findings are reliable as diseased and healthy controls were included, psoriasis patients were not receiving any treatment and validated methods and tools were used.

To conclude, in line with literature, psoriasis seems to be related to higher depression, anxiety, and poorer QoL which are correlated with disease severity. Effective disease control significantly reverses psychosocial burden of disease. Serum proBDNF levels and proBDNF/BDNF ratio have a relation both with clinical response and improvement in subjective scales. Therefore, the role of proBDNF and proBDNF/BDNF ratio as potential biomarkers for depression or indicators of improvements of psychological parameters deserves being further investigated.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## AUTHOR CONTRIBUTIONS

Conception: Hasan Aksoy, Tülin Ergun, Hakan Yöney. Design: Tülin Ergun, Hasan Aksoy, Dilek Seckin Gencosmanoglu. Supervision: Tülin Ergun, Hasan Aksoy. Data collection and/or processing: Hasan Aksoy, Tülin Ergun. Biochemical procedures: Mustafa Akkiprik, İrem Peker Eyuboglu. Analysis: Hasan Aksoy, Gülru Pemra Cöbek Unalan, Tülin Ergun. Literature review: Tülin Ergun, Hasan Aksoy. Writing: Tülin Ergun, Hasan Aksoy. Critical review: Tülin Ergun, Hasan Aksoy, Dilek Seckin Gencosmanoglu.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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