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Serum VEGF levels in major depression and the effect of antidepressant treatment

Ozlem Olguner Eker[1], Koksal Dinc[1], Akif Asdemir[1], Eser Kilic[2], Ertugrul Esel[1]

[1]Erciyes University, Faculty of Medicine, Department of Psychiatry, Kayseri, Türkiye
[2]Erciyes University Faculty of Medicine, Department of Medical Biochemistry,Kayseri, Türkiye

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Abstract

Identifying reliable biomarkers for depression remains a major research focus. Vascular endothelial growth factor (VEGF) has been proposed as a candidate due to its involvement in neurovascular processes. This study evaluated the diagnostic and therapeutic significance of VEGF in major depressive disorder (MDD). This prospective, observational case–control study was conducted at a single academic center between July 2022 and June 2023. The sample comprised 17 patients with MDD and 30 healthy controls. Depression severity was assessed using the Hamilton Depression Rating Scale. Serum VEGF levels were measured with enzyme-linked immunosorbent assay (ELISA) at two time points in patients (during a depressive episode and after treatment response), while controls underwent a single measurement. Analyses were adjusted for potential confounders, including age, body mass index, smoking, and prior antidepressant use. VEGF levels did not significantly differ between patients and controls. However, post-treatment VEGF levels in patients were significantly lower than those of controls. No significant within-group change was observed between pre- and post-treatment measurements in patients. These findings provide limited support for the neurotrophic hypothesis of depression. The observed post-treatment decline in VEGF suggests a complex regulatory mechanism rather than a simple neuroprotective effect. Given the small sample size and reliance on peripheral VEGF measurements, larger studies incorporating central VEGF assessments are needed to clarify its role in depression.

Keywords: Depression, vascular endothelial growth factor, biomarker, neurotrophic hypothesis

Introduction

Depression is a mental disorder affecting millions globally, significantly increasing disability rates among adolescents and adults [1]. Diagnosis currently depends largely on clinical examinations by evaluating present symptoms. Thus, identifying biological markers assisting in diagnosis or influencing treatment choice in depression is crucial.

The neurotrophin hypothesis in depression suggests that decreased neurotrophic activity and neurogenesis in the brain areas where emotional and cognitive processes are formed may lead to depression [2,3]. It is thought that growth factors play a role in functions such as neurogenesis, neuron growth, differentiation and neurotransmitter production in some structures of the brain, and that these functions play a role in the etiology of depression. Animal studies report various internal and external factors, such as cortisol levels, serotonergic transmission, stress, and environmental stimuli, may induce depression by causing changes in hippocampal neurotrophic factor levels and volume. These alterations can be reversed with antidepressants [4]. Among individuals diagnosed with Major Depressive Disorder (MDD), changes have been observed in growth factor levels, like Brain-Derived Neurotrophic Factor (BDNF), Insulin-like Growth Factor-1 (IGF-1), Fibroblast Growth Factor (FGF), Vascular Endothelial Growth Factor (VEGF), and Neuron Growth Factor in peripheral or central nervous system levels. Antidepressants appear to normalize these levels [5]. Despite the extensive focus on BDNF in MDD neurobiology, effects of VEGF should not be overlooked [6]. Decreased levels of neurotrophic factors like BDNF and/or VEGF have been associated with neuronal atrophy

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Corresponding Author: Ozlem Olguner Eker, Erciyes University, Faculty of Medicine, Department of Psychiatry, Kayseri, Türkiye
Email: ozlemolgunereker@erciyes.edu.tr

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in MDD-related brain regions [7]. From these findings, it is proposed that growth factors synthesized in the CNS like BDNF, FGF-2, IGF-1, and VEGF play roles in adult neurogenesis and are involved in the pathophysiology of depression and the mechanism of action of antidepressants [8].

VEGF, considered as an angiogenic cytokine, is synthesized in endothelial cells, macrophages, activated platelets, T lymphocytes, smooth muscle cells, renal cells, keratinocytes, osteoblasts, cancer cells, and brain cells. VEGF stimulates endothelial cell proliferation and survival, new vessel formation, nitric oxide-related vasodilation, and increases vascular permeability [9]. It is also proposed to be a common regulatory factor in both angiogenesis and neurogenesis in the brain [10]. Studies have revealed VEGF's neurotrophic and neuroprotective effects in the central nervous system [11]. VEGF plays a crucial role in hippocampal neurogenesis and depression by influencing pathophysiological processes, supporting the development of hippocampal neurons, and safeguarding stress-related neurons from damage. This is significant for antidepressant treatment [12]. A systematic review of studies in rodents has shown that ketamine rapidly increases VEGF release in the prefrontal cortex (PFC) and hippocampus, thereby supporting synaptogenesis and neurogenesis in these regions [13]. VEGF is believed to exhibit its neurogenic effects either by stimulating endothelial cell proliferation or by prompting the release of other neurotrophic factors from endothelial cells [14].

In MDD, volume reductions in certain brain structures due to neuron and glia loss are thought to be potentially associated with malfunctions in the functions of neuron and vascular growth factors like VEGF [15]. Findings suggesting that VEGF has a role in depression are as follows: VEGF dysregulation being related to suicide risk [16], chronic stress reducing BDNF and/or VEGF expression and function in the PFC and hippocampus, affecting the stress response [17], increased BDNF and VEGF expression with antidepressant treatment [14], and animal studies showing BDNF's antidepressant-like behavioral effects being dependent on VEGF release from excitatory neurons in the PFC [18]. As angiogenesis and neurogenesis are thought to be concurrently impaired in MDD, it is proposed that VEGF could act as a common regulatory factor in the pathophysiology of depression [8].

Conflicting data has emerged from existing clinical studies on the relationship between VEGF and MDD. Some studies reported increased [19], decreased [20], or unchanged [21] VEGF levels in depressed patients compared to healthy controls. These discrepancies might arise from significant differences in study populations, factors like age, gender, body mass index, total number of depression episodes (i.e., recurrent vs. acute), accompanying disorders, and genetic variability [22]. VEGF may predict response to antidepressant treatment, suggesting its potential role as a biomarker and mediator in neuroplastic processes [19]. More recently, a large case–control study reported that circulating VEGF-A is lower in patients during a major depressive episode and remains reduced relative to healthy controls even after 3–6 months of antidepressant therapy, underscoring a persistent VEGF deficit in MDD [23]. Regarding somatic treatments, electroconvulsive therapy (ECT) appears to induce transient, session-related increases in plasma VEGF within hours after individual seizures, without sustained baseline elevation across the treatment series or a clear association with clinical outcome [24]. By contrast, repetitive transcranial magnetic stimulation (rTMS) studies suggest that clinical responders/remitters show increases in serum VEGF and that the magnitude of VEGF change tracks symptom improvement—particularly reductions in anhedonia—supporting VEGF as a treatment-sensitive biomarker of neuroplasticity [25,26].

This study aimed to determine whether serum VEGF concentrations are altered in patients with MDD, whether further modifications occur in response to antidepressant treatment, and whether VEGF can serve as a potential diagnostic or therapeutic biomarker for major depression. Serum VEGF concentrations were measured in patients with major depression both before and after treatment and compared with those of healthy controls. We hypothesized that serum VEGF levels would differ between patients with MDD and healthy controls, and that antidepressant treatment would further modulate VEGF concentrations.

Material and Methods

Study Design and Participant

This study was originally conducted as a prospective, observational case–control investigation at Erciyes University Faculty of Medicine between 2016 and 2017. The protocol was first approved by the Ethics Committee of Erciyes University Faculty of Medicine on December 17, 2016 (Approval No: 96681246/193), after which patient recruitment commenced. Additional approval for the publication of these data was obtained from the same committee on July 27, 2022 (Approval No: 2022/509). All procedures were carried out in accordance with the ethical standards of the Declaration of Helsinki. Written informed consent was obtained from all participants before enrollment.

A total of 30 patients meeting DSM-5 criteria for MDD were consecutively recruited. Following treatment response, 13 patients were lost to follow-up, yielding a final patient cohort of 17 individuals (5 males, 12 females; age range 18–65 years). At baseline, 9 patients were receiving venlafaxine, 3 fluoxetine, 3 sertraline, and 2 paroxetine; all were experiencing an active depressive episode. The control group comprised 30 age- and sex-matched healthy volunteers (8 males, 22 females) without personal or family history of psychiatric or systemic illness; each underwent the same clinical and laboratory screening as patients.

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The inclusion criteria were age 18–65 years; a primary diagnosis of MDD according to DSM-5; active depressive episode at study entry; and provision of written informed consent. Exclusion criteria comprised menstrual irregularities, pregnancy or suspected pregnancy, or current hormonal therapy in female participants; established cardiovascular disease; electroconvulsive therapy within the previous six months; diagnosed metabolic or endocrine disorders; current substance abuse or dependence (excluding tobacco); history of significant head trauma; and neurological conditions (e.g., epilepsy) associated with organic brain pathology. To account for potential confounders, age, body mass index (BMI), daily cigarette consumption, and prior antidepressant use were recorded for all participants.

Clinical Assessments

Depressive symptom severity was measured using the Hamilton Rating Scale for Depression (HRSD) at two time-points—baseline (pre-treatment) and upon achieving a clinically defined treatment response (≥ 50 % reduction in HRSD score). Healthy controls were assessed once at enrollment.

Blood Sample Collection and VEGF Measurement

Venous blood samples were collected between 08:00 and 10:00 AM following an overnight fast of at least 8 hours. Serum was separated and stored at – 80 °C until analysis. VEGF concentrations were quantified via enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions. Serum VEGF concentrations were measured using an ELISA reader (Sunrise Basic, Tecan Austria GmbH) and a commercially available human VEGF ELISA kit (Novex Life Technologies, USA). The detection range of the assay was 0–1500 pg/mL, with a sensitivity of <5 pg/mL. Optical density values were converted to serum concentrations according to the standard curve, and data were analyzed using Curve Expert 1.3 software as recommended in the kit manual. The timing of assessments and patient attrition are summarized in Figure 1.

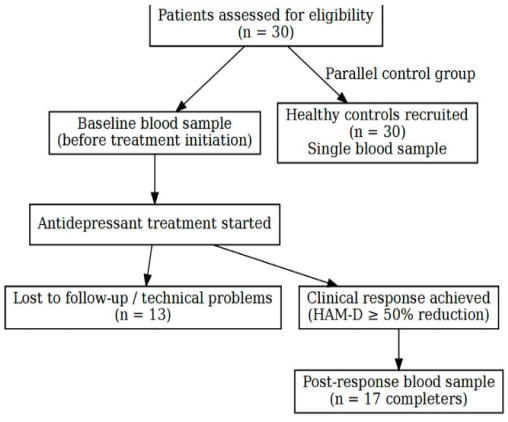

Figure 1. Flowchart of patient enrollment, follow-up, and VEGF assessments

Statistical Analysis

Data distribution was assessed by the Kolmogorov–Smirnov test and by inspection of histograms and boxplots. Normally distributed variables are presented as mean±SD and compared by independent-samples t-test; non-normally distributed variables are reported as median (25th–75th percentiles) and compared by Mann–Whitney U test; categorical data are expressed as n (%) and analyzed with the χ^2 test. Within-group comparisons (baseline vs. post-treatment) used paired t-tests for HRSD scores and the Wilcoxon signed-rank test for VEGF levels. To adjust for age, BMI, and smoking status, analysis of covariance (ANCOVA) was applied when comparing VEGF between groups. Correlation analyses employed Pearson's r for parametric and Spearman's ρ for nonparametric data. A two-tailed $p<0.05$ was considered statistically significant. All analyses were performed using IBM SPSS Statistics 23.0.0.3 (IBM Corp., Armonk, NY, USA).

Additionally, a post-hoc power analysis was conducted using G*Power 3.1 for the primary comparison (patients post-treatment vs. controls). Based on the observed effect size (Cohen's d=0.66) and α=0.05 (two-tailed), the achieved power was calculated as 56% (patients n=17, controls n=30).

Result

Sociodemographic and Clinical Characteristics

A total of 30 patients were initially enrolled in the study; however, 13 patients were lost to follow-up as they did not attend subsequent visits, and due to technical problems during VEGF serum assay, VEGF measurements could not be obtained for these patients. Therefore, the final analyses were conducted on 17 patients who completed the study. The patient and control groups did not differ significantly in gender distribution (patients: 29.4% male vs. controls: 26.7% male; $\chi^2(1)=0.041$; $p=0.840$) or smoking status (patients: 41.2% smokers vs. controls: 36.7% smokers; $\chi^2(1)=0.093$; $p=0.760$). However, patients were significantly older (43.64±10.58 vs. 37.60±8.50 years; $t(45)=2.142$; $p=0.038$), had a higher body mass index (31.64±5.48 vs. 26.99±4.93 kg/m²; $t(45)=2.981$; $p=0.005$), and fewer years of education (7.64±4.51 vs. 12.53±3.28 years; $t(45)=–4.270$; $p<0.001$) than controls (Table 1).

Comparison of VEGF Levels

Within the MDD group, serum VEGF concentrations did not change significantly from baseline (133.02±105.70 pg/mL) to post-treatment (78.66±97.46 pg/mL) (Wilcoxon signed-rank test: $z=–1.870$; $p=0.062$). After adjusting for age, BMI, and daily cigarette consumption via ANCOVA, baseline VEGF levels in patients were comparable to controls (154.87±125.18 pg/mL; $F(1.42)=0.489$; $p=0.488$). In contrast, post-treatment VEGF levels in the patient group were significantly lower than in the control group ($F^*(1.42)^*=5.046$; $p=0.030$) (Table 2).

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Table 1. Sociodemographic characteristics of patient and control groups

Variables	Patient Group (n=17)	Control Group (n=30)	Comparison (Independent samples t-test and Chi-square test)
Age (year)	43.64±10.58a	37.60±8.50	t=2.142; df=45; p=0.038
Education (year)	7.64±4.51b	12.53±3.28	t=-4.270; df=45; p<0.001
BMI (kg/m2)	31.64±5.48a	26.99±4.93	t=2.981; df=45; p=0.005
Smoking	Present: 7 (41.2%) Absent: 10 (58.8%)	Present: 11 (36.7%) Absent: 19 (63.3%)	$\chi2$=0.093; df=1; p=0.760
Gender	Female: 12 (70.6%) Male: 5 (29.4%)	Female: 22 (73.3%) Male: 8 (26.7%)	$\chi2$=0.041; df=1; p=0.840

a: Higher than controls, b: Lower than controls, n: Number of subjects, BMI: Body Mass Index

Table 2. Serum VEGF levels in patients and controls

Group	VEGF (pg/mL), Mean±SD	Comparison	p-value
Patients – Baseline (n=17)	133.02±105.70	Controls (n=30)	0.488[1]
Patients – Post-response (n=17)	78.66±97.46	Controls (n=30)	0.030[1]
Change from Baseline to Post-response	—	Within-patient comparison	0.062[2]

p-values adjusted for age, BMI, and daily cigarette consumption using ANCOVA. Wilcoxon signed-rank test

Correlation Analysis

In patients with MDD at baseline, VEGF concentrations did not correlate significantly with age (Pearson's r=–0.056; p=0.831), BMI (r=–0.034; p=0.898), or daily cigarette consumption (r=0.145; p=0.579).

Discussion

The key findings of this study indicate that (i) there was no statistically significant difference in VEGF concentrations between individuals with depression and healthy controls during the depressive episode; however, following treatment response, VEGF concentrations were significantly lower in patients compared to controls, and (ii) VEGF concentrations did not exhibit a significant change before and after treatment within the patient group. These results suggest that the role of VEGF in depression is intricate, highlighting the multifaceted nature of its relationship with the disorder.

VEGF is a growth factor that is essential for vascular permeability in the vascular system, as well as for neurogenesis, angiogenesis, and synaptic plasticity in limbic structures of the brain. Therefore, it is thought that growth factors may contribute to the pathophysiology of depression and the response to antidepressants [27].

Studies on VEGF levels in MDD differ from each other in terms of results. In our study, serum VEGF levels did not differ significantly between patients with depressive episodes and controls. While this result aligns with findings from some previous studies [21,28–31], it differs from the results of others [19,20,23,32]. In fact, when the literature is examined, it is seen that the majority of studies report increased VEGF levels in depression, indicating the opposite of the neurotrophic hypothesis [19,33–35]. Similar to our study, another study involving patients with depressive episodes who were using medication reported no significant variation in VEGF levels between the patient and control groups [30]. VEGF levels in this study were measured solely at the peripheral level, without examination of central levels. Plasma VEGF concentrations and VEGF concentrations in the brain may not be related to each other [36]. As far as we know, there are no clinical studies investigating the association between brain and plasma VEGF levels. Nonetheless, a study on a mouse model of depression found decreased VEGF-A levels in the brain but no significant alteration in serum levels [37]. The inconsistency between study results is due to the fact that the clinical characteristics of the patient groups, such as demographics and disease severity, differ between studies, and depression itself is clinically heterogeneous. It may be due to different disorders or medication use.

Although VEGF levels did not change before and after treatment among patients with depression in this study, the observation that post-treatment VEGF levels were lower than those of controls suggests that either antidepressant treatment or improvement in depression may reduce VEGF levels below normal. It is reported in the literature that VEGF levels after response to treatment are lower than normal. There are studies where it decreases compared to controls [23,38]. In a study by

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Iga et al. (2007), it was suggested that MDD patients initially exhibited significantly elevated peripheral leukocyte VEGF mRNA expression compared to healthy controls, and that the reduction observed after eight weeks of treatment might serve as a predictor of clinical improvement [32]. There is an increase in neurodegenerative and oxidative load during the depressive episode [39], therefore, it can be thought that a compensatory increase in VEGF level develops to reduce this burden during the episode [33]. Therefore, it can be concluded that both depression scores and VEGF levels decrease as a result of the elimination of this burden with antidepressant treatment [40].

Recent large-scale case–control studies, however, have reported that VEGF-A may actually be lower in depressed patients compared to healthy controls, and importantly, that this reduction persists even after several months of antidepressant therapy [23]. This suggests that antidepressants alone may not normalize VEGF deficits in MDD. On the other hand, interventional treatments such as ECT and rTMS seem to influence VEGF more dynamically. ECT has been shown to trigger transient, session-related increases in plasma VEGF within hours of treatment, although sustained changes are usually not observed [24]. In contrast, rTMS appears to induce VEGF increases in responders, with the magnitude of VEGF change correlating with clinical improvement and, in particular, reduction in anhedonia [25,26]. These findings indicate that VEGF may serve not only as a marker of disease state but also as a potential biomarker of treatment response, especially in neurostimulation therapies.

In the literature, the possible harms of VEGF in the etiopathogenesis of some neuropsychiatric and vascular diseases are mentioned. In a study conducted on rats, when an ischemic brain model was experimentally created with cranial vascular occlusion and then recombinant VEGF was applied in increasing doses, it was observed that neuronal damage occurred instead of a neuroprotective effect after a threshold value [41]. It has also been suggested that chronic VEGF infusion in rats may cause vasogenic brain edema [42]. Another study claims that inhibition of VEGF in the early stages in rats with cerebral ischemia may reduce the infarct area and contribute to behavioral recovery [43]. It has been reported that there is an increased and harmful inflammatory pattern in depression patients and that the blood-brain barrier is affected by this high degree of inflammation and suffers neurotoxic damage [44]. It is also suggested that VEGF contributes to pathological processes, including inflammation and neurodegeneration, within the neurovascular structure by enhancing blood-brain barrier permeability [45].

The conclusion that can be drawn from all these data is that the increase in VEGF levels may facilitate neurovascular damage after a point and cause neuronal damage instead of having a neuroprotective effect. Therefore, considering that depression has a neurodegenerative aspect, we can conclude that in order for the supposed improvement in pathological processes to occur, the VEGF effect must be suppressed to the threshold level necessary to ensure neurovascular integrity. It can be suggested that even normal levels of VEGF levels in patients with depression may cause the mentioned negative effects due to impaired blood-brain barrier permeability, and that improvement with treatment may be related to the treatment preventing its damaging effect by reducing VEGF levels below normal.

Limitations and Future Directions

This study has several limitations. The small sample size may have limited the statistical power, as demonstrated by our post-hoc power analysis, which indicated an achieved power of only 56%. Moreover, the study initially enrolled 30 patients, but 13 were lost to follow-up and could not be included in the final analyses due to both non-attendance and technical problems during VEGF assay, resulting in a final sample of 17 patients. This attrition further reduced the generalizability of the findings. Another limitation is the heterogeneity of antidepressant medications used at baseline (venlafaxine, fluoxetine, sertraline, paroxetine). Due to the small sample size, subgroup analyses by medication type, dose, or duration were not feasible, which may have confounded VEGF levels. In addition, the lack of detailed information on antidepressant dosage and treatment duration may also have influenced VEGF levels. Furthermore, as VEGF was only measured peripherally, its central effects remain unclear.

Future studies should incorporate larger, multi-center cohorts, longitudinal follow-ups, and cerebrospinal fluid or neuroimaging analyses to better understand VEGF's role in depression.

Conclusion

This study investigated the potential role of VEGF as a biomarker for major depressive disorder. Our findings indicate that serum VEGF levels in patients during the depressive episode were not significantly different from those of healthy controls. However, after treatment response, VEGF levels in patients were significantly lower than those in controls. These findings suggest that VEGF may not be a reliable biomarker for the diagnosis of depression but could potentially be used to monitor treatment response.

These results do not fully align with the neurotrophic hypothesis, which suggests that increased VEGF levels may contribute to neuronal repair and recovery in depression. However, if we consider the alternative hypothesis that excessive VEGF activity may contribute to neurovascular damage, then our findings may partially support the idea that reducing VEGF levels after treatment might play a role in recovery.

In conclusion, while VEGF does not appear to be a diagnostic biomarker for depression, its post-treatment decline suggests that it may have potential utility in assessing treatment response. Further research with larger sample sizes and more comprehensive methodologies is necessary to determine its clinical relevance.

Conflict of Interests

The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical Approval
This study was approved by the Erciyes Universty Faculty of Medicine on (27/07/2022) with document number (2022/509).

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