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Serum BDNF and suicidal ideation in drug-naïve and drug-treated MDD patients: a case–control study

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Abstract

Background: Disturbances in structural and synaptic plasticity have been linked to depression and suicidal ideation. One of the major neurotrophic factors, the brain-derived neurotrophic factor (BDNF), is involved in the maintenance and survival of neurons and synaptic plasticity. This case–control study assesses the serum BDNF and suicidal ideation among drug-naïve and drug-treated MDD patients attending university hospitals and comparing them to healthy control. A simple random sample of 57 MDD patients and 57 age- and sex-comparable controls were enrolled. The researchers conducted a semi-structured interview to collect the demographic characteristics and disease history. Structured Clinical Interview for DSM-5 (SCID-5), Hamilton Depression Rating Scale (HDRS), and Beck Scale for Suicidal Ideation (BSS) were applied to the participants. Blood samples were collected to measure plasma BDNF level.

Results: The MDD group had lower BDNF than the control group. Within the MDD group, drug-naïve patients had significantly lower BDNF than drug-treated patients. Female patients had lower BDNF than male patients. Positive family history of MDD was associated with low BDNF. Severe and moderate cases had lower BDNF than mild cases. High BSS (≥24) was associated with low BDNF. A statistically significant positive correlation was found between BDNF and age, disease duration, duration of the current episode, and the number of previous episodes.
On the other hand, a statistically significant negative correlation was found between BDNF and age of MDD onset, HDRS, and BSS. A regression model was highly statistically significant in the prediction of HDRS. BDNF and disease duration were negatively correlated with HDRS. On the other hand, depression treatment status was not significantly associated with the HDRS prediction model.

Conclusion: Our findings extend the neurotrophic concept of depression by identifying the decreased BDNF levels as a peripheral biomarker of MDD. Our assessment of depression and suicidal ideation (SI) and their relationship to decreased BDNF levels shed light on the etiopathology of MDD and its related suicidality. They should be more studied to understand better the mechanisms by which they develop. To further explore the effect of BDNF in suicide, larger study sizes and a range of psychiatric diagnoses associated with suicide attempts are required.

Keywords: BDNF, Suicidal ideation, MDD, Drug-naïve, Drug-treated, Neurogenesis, Neuroplasticity

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Background

One of the world's most prevalent and most disabling mental disorders is major depressive disorder (MDD). Depression is the fourth leading cause of disability (measured in life years of disability-adjusted). According to the Global Burden of Disease Study, the prevalence of MDD for the lifetime is 15%. According to the WHO, MDD is the second leading global cause of death by 2020 [1].

According to the biopsychosocial model, MDD is caused by a combination of biological, psychological, and social variables [2]. According to the diathesis-stress concept, depression occurs when stressful life events trigger an underlying susceptibility. This susceptibility could be genetic, indicating a balance of nature and nurture, arising from worldviews acquired throughout childhood [3]. Numerous individual genetic variations are thought to have an effect on MDD. In 2018, exhaustive genome research identified 44 variations in the genome associated with an increased risk of depression [4]. In 2019, a recent study discovered 102 genetic variations associated with MDD [5].

The etiopathogenesis of MDD is assumed to be complex and poorly understood. MDD is associated with a number of pathophysiological mechanisms, including the immune system, autonomic nervous system, hypothalamic–pituitary–adrenal axis, and specific brain processes, particularly monoaminergic brain circuitries and the neurotrophic supporting route. Yet, no biomarker has been established that can significantly increase the precision of the diagnosis, directing therapy choices or response, or reliably anticipating the outcome [6].

The "monoamine hypothesis" has been the prevailing biochemical hypothesis of depression for many years. However, the failure of numerous individuals to respond to antidepressants that restore monoamines and the clinical delay of therapeutic response many weeks were among the evidence against this notion [7].

Duman and his colleague [8] presented the "neurotrophin theory of depression" as a possible biochemical basis underlying depression. This concept hypothesized that depression was caused by abnormal neurogenesis in areas of the brain associated with emotion and cognition [8].

Based on this theory, stressor exposure could lead to a decrease in the expression of neural growth factors (neurotrophins), which are a class of proteins that promote neuronal survival, development, and differentiation, that results in decreased hippocampus neurogenesis, atrophy of the neuron, and loss of the glial cell [9].

The BDNF factor is a neurotrophic molecule that modulates brain neuroplasticity and is among the most widely examined molecules in psychiatric disorders, which controls the growth and survival of the neurons throughout life by stimulating three pathways: MAPK, phospholipase C, and phosphoinositide 3-kinase through binding to its receptor tropomyosin receptor kinase B (TrkB), which mediates BDNF's primary neurogenesis and neuroprotective functions [10].

The neurotrophic depression hypothesis depends on the connection between decreased BDNF levels and the increased prevalence of depression with more severe symptomatology associated with neuronal death and cortical atrophy. Most antidepressant effects are postulated due to increased BDNF expression and concentration, which improves neuronal plasticity. In cell propagation sites, such as the dentate gyrus' subventricular and subgranular zones, which maintain a stable mood, this latter process is critical [11].

BDNF is generated in the brain as a pro-protein (pro-BDNF), particularly in the hippocampus and hypothalamus. Following that, pro-BDNF is processed to yield mature BDNF and pro-peptide. The imbalance of pro-BDNF and mature BDNF is thought to contribute to neuronal degeneration and subsequent psychiatric disorders, mainly MDD [12].

The human BDNF gene is located on chromosome 11p13. This gene has many variants and several single-nucleotide polymorphisms (SNPs). Val66Met polymorphism that modulates the secretion of BDNF by neuron is the most studied BDNF SNP. Some opinions suggest that the BDNF Val66Met polymorphism is not associated with depressive disorders per se [13]. Still, a number of factors as gene–gene interaction may affect its involvement in depression, particularly, BDNF gene interaction with the serotonin transporter-linked polymorphic region (*5-HTTLPR*) that encodes 5-HTT [14]. In the study of Martinowich and Lu, they found that the serotonin (*5-HT*)–*BDNF* systems act synergistically on synaptic plasticity and neurogenesis in brain areas implicated in depression [15].

BDNF epigenetics could also be involved in the pathogenesis of depression [16]. Methylation of the DNA of the *BDNF* gene is one of the most studied epigenetics. Elevated methylation was found at the exon IX and I of BDNF in MDD patients than in healthy controls [17]. Another epigenetic effect is induced by microRNAs, which control the several gene expression of mRNAs. The serum BDNF level and microRNAs have an inverse association in depressed patients. Moreover, the serum levels of microRNAs were predominantly elevated in MDD patients compared with healthy controls [18].

MDD patients had decreased serum concentrations of BDNF than healthy subjects. It has been postulated that the reduced serum and plasma levels of BDNF in depressed patients, but not in whole-blood BDNF, are associated with BDNF release and secretion processes regardless of platelet reactivity [16].

Suicide is a significant health problem in the twenty-first century. It affects around 800,000 individuals every year. According to the World Health Organization, suicidality is a prominent cause of injury and mortality worldwide, being the second largest cause of death in the age of 15 to 29 years old. Suicidal behavior is influenced by various variables, including the interactions between personality, psychosocial and environmental circumstances, and inheritance. There are multiple risk factors for suicidality. Psychiatric disorders (especially mood disorders) seem to be the most critical. It is believed that up to 60% of those who commit suicide had the diagnosis of MDD [19].

Serum BDNF levels appear to be very low, especially in patients who have attempted suicide. The data supporting BDNF's role in suicide extends from human postmortem brain research of suicide victims to research of persons who had suicidal attempts or thoughts [19]. In suicidal individuals, it seems that BDNF expression and function are downregulated. Numerous mechanisms might be postulated to account for the reduction in DNA expression and serum BDNF levels. As previously shown, the distinct methylation in exon IX and exon I may be one of the processes involved. The downregulation of the TrkB signaling has been observed in suicidal patients [17].

The BDNF pathway is also known to be affected by drugs; for example, cyclosporine could lower BDNF and the expressions of TrkB mRNA in the immunosuppressant with depression. Besides, antidepressant therapy has shown increased levels of BDNF [11].

BDNF's research included the recent advancement of the techniques of its investigations. BDNF research ranges from the quantization of the protein, RNA expression, the sequencing of DNA, and, finally, epigenetic research [20].

Even so, some critical questions need to be answered, such as whether disturbances in BDNF continue past the clinically depressed state, whether BDNF values are associated with clinical characteristics of depression, and whether different antidepressants influence BDNF levels similarly.

Aim of the study

This study investigates the serum BDNF and suicidal ideation among drug-naïve and drug-treated MDD patients attending the University Hospitals and comparing them to healthy control.

Methods

Study design and setting

We performed this case–control study from 1 January to 30 March 2021 on patients attending The University Hospital.

Subjects

This study enrolled a simple random sample of 57 MDD patients and 57 age- and sex-comparable controls. Patients had to fulfill the following requirements to participate in the study: they must have the diagnosis of MDD according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [21], be 18 years or older, and agree to participate in the research. We excluded from the study the subjects with a history of other psychiatric disorders, having a comorbid psychiatric disorder, having a neurological disease, or patients diagnosed with dementia. Participants in the control group must not have a diagnosis of MDD according to DSM-5 and met the above exclusion criteria.

Patient group

Fifty-seven MDD patients from different social and educational classes were recruited from the attendee in the university hospital's psychiatric outpatient clinic or ward.

Subdivided into:

Drug-naïve group: 28 newly diagnosed patients without the previous intake of antidepressants.
On treatment group: 29 patients on antidepressant treatment for at least 6 months.

Control group

Fifty-seven matched healthy subjects. They were workers in the university hospital and visitors of the hospitalized patients other than the psychiatric department.

Sample size

We assumed that the serum level of a BDNF in the major depressive disorder group versus a control group is 31.0 ± 8.2 versus 34.7 ± 5.6 (ng/ml) [22], the confidence level 95%, and the power 80%. The total sample size is 114 (divided into 57 in each group). It was calculated by Open Epi [23].

Data collection

A semi-structured interview was conducted by the researchers to gather the demographic characteristics, which includes age, sex, marital status, education, occupation, and the history of the disorder in MDD groups like age of onset, duration of the disorder, duration of current episode, and the number of previous episodes.

Structured Clinical Interview for DSM-5 (SCID-5) is used for the diagnosis of MDD. The SCID-5 is a structured interview that diagnoses the major DSM-5 diagnoses like mood disorders, psychotic disorders, and others. It is performed by a psychiatrist or other qualified mental health specialist knowledgeable about the DSM-5 classified disorders and their diagnostic criteria. It can

be used with psychiatric or general care patients or non-patients, such as participants in a group study of mental disease or family members of psychiatric patients. There are three distinct SCID-5 versions for diagnosing DSM-5's primary diagnoses; two distinct SCID-5 versions assess personality disorders as described in DSM-5 [24].

Hamilton Depression Rating Scale (HDRS) is used to assess the severity of depression by answering 21 questions. Patients with mild depression have a score of 13 to 16, while those with moderate depression scored from 17 to 19, and finally, to have severe depression, patients must score 20 to above. The Arabic version has a high Cronbach's alpha (0.86) [25].

Beck Scale for Suicidal Ideation (BSS): this scale is used to assess suicide risk. It is a self-report scale consists of 19 items. Its scores range from 0 to 48. There is no specific cut-off for this scale, but obtaining higher scores indicates more suicide risk [26]. We used a cut-off ≥24 in this study [27]. The Arabic version has a high Cronbach's alpha (0.91) [28].

The measurement of BDNF: 4 ml of blood sample was taken, then centrifuged. The Human BDNF Immunoassay Quantikine® ELISA Kit (R, D Systems GmbH, Wiesbaden-Nordenstadt, Germany) was used to measure the serum level of BDNF [29]. Upon the manufacturer's instructions, ELISA assays were done, at the clinical pathology department, university hospitals.

Statistical analysis

SPSS software version 27 was used for the statistical analysis [30]. Data were presented in tables and figures. Mean, median, standard deviation, and range were used for showing the quantitative variables. At the same time, the frequencies and proportions were utilized for presenting the qualitative variables.

For the determination of the homogeneity of the distribution characteristics of variables and variance, we used the Shapiro–Wilk test.

When appropriate, we used the Student's t-test and Mann–Whitney U test for analyzing the quantitative variables between two groups.

We used Pearson's chi-squared test and chi-square for linear trend as appropriate for analyzing the qualitative variables.

For analyzing the continuous data between more than two groups, we used Kruskal–Wallis H (KW) tests. Spearman's correlation coefficient was used to analyze the linear relationship between quantitative variables.

Multiple linear regression was done to determine predictors of HDRS and to exclude confounding factors. Dubrin–Watson test (DW) was used for autocorrelation of the prediction errors in the regression model. A value of DW between 1.5 and 2.5 was considered normal [31]. A P-value of ˂0.05 was considered statistically significant in all tests, and a P-value of ˂0.001 was accepted as highly statistically significant.

Results

Sociodemographic characteristics of the study participants are presented in Table 1. There was no statistically significant difference between the MDD group and the control group in demographic characteristics. MDD patients were classified as drug-naïve and drug-treated patients. The two subgroups are compared according to disease characteristics in Table 2. There was a highly statistically significant difference between drug-naïve patients and drug-treated patients in HDRS total score, depression severity, and suicidal ideation. Drug-naïve patients had higher HDRS total score, more severe depression, and more suicidal ideation than drug-treated patients.

The serum level of BDNF was compared among the studied groups in Fig. 1. There was a highly statistically significant difference between the study groups in BDNF. The MDD group had lower BDNF than the control group. Within the MDD group, drug-naïve patients had significantly lower BDNF than drug-treated patients.

There were statistically significant associations between BDNF and some characteristics of the MDD group (Table 3). Female patients had lower BDNF than male patients. Positive family history of MDD was associated with low BDNF. High BSS (≥24) was associated with low BDNF.

In addition, there were statistically significant associations between BDNF and characteristics of the MDD group. Female patients had higher HDRS than male patients. Married patients had higher HDRS than not married patients. Positive family history of MDD was associated with high HDRS. High BSS (≥24) was associated with high HDRS. There was a highly statistically significant difference between drug-naïve patients and drug-treated patients in HDRS total score. Drug-naïve patients had higher HDRS total score. Severe and moderate cases had lower BDNF than mild cases.

BDNF was negatively correlated with HDRS and BSS (Figs. 2 and 3). On the other hand, HDRS and BSS were positively correlated (Fig. 4).

There was a statistically significant positive correlation between BDNF and age, disease duration, duration of the current episode, and the number of previous episodes (Table 4). On the other hand, there was a statistically significant negative correlation between BDNF and age of MDD onset.

A regression model was highly statistically significant in the prediction of HDRS. BDNF and disease duration was negatively correlated with HDRS (Table 5). On the other hand, depression treatment status was not significantly associated with the HDRS prediction model.

Table 1 Demographic characteristics of the studied groups

Variables	MDD group (*n* = 57)	Control group (*n* = 57)	P
Age (years)			
Mean ± SD	32.5 ± 5.6	30.1 ± 7.4	0.06
Sex			
Males	19 (33.3%)	22 (38.6%)	0.6
Females	38 (66.7%)	35 (61.4%)	
Marital status			
Single	15 (26.3%)	24 (42.1%)	0.1
Married	32 (56.1%)	28 (49.1)	
Divorced	5 (8.8%)	0 (0.0%)	
Widow	5 (8.8%)	5 (8.8%)	
Education			
Illiterate, elementary	4 (7.0%)	5 (8.8%)	0.9
Preparatory	5 (8.8%)	5 (8.8%)	
Secondary	24 (42.1%)	20 (35.1%)	
High education	24 (42.1%)	27 (47.4%)	
Occupation			
Working	24 (42.1%)	28 (49.1%)	0.5
Not working	33 (57.9%)	29 (50.9%)	

MDD major depressive disorder

Table 2 Clinical characteristics of the MDD group

Variables	Drug-naïve patients (*n* = 28)	Drug-treated patients (*n* = 29)	P
Age of onset (years)			
Mean ± SD	21.1 ± 3.5	20.5 ± 2.7	0.5
Family history			
Positive	18 (64.3%)	21 (72.4%)	0.5
Negative	10 (35.7%)	8 (27.6%)	
Disease duration (years)			
Mean ± SD	10.3 ± 3.5	13.1 ± 7.3	0.8
Duration of the current episode (days)			
Mean ± SD	14.0 ± 3.1	15.4 ± 4.1	0.2
Number of previous episodes			
Median (range)	5 (3 – 9)	5 (3 – 11)	0.5
Depression severity			
Mild	6 (21.4%)	19 (65.5%)	< 0.001
Moderate	6 (21.4%)	9 (31.0%)	(HS)
Severe	16 (57.1%)	1 (3.4%)	
Suicidal ideation			
BSS < 24	12 (42.9%)	28 (96.6%)	< 0.001
BSS ≥24	16 (57.1%)	1 (3.4%)	(HS)

BSS Beck Scale for Suicidal Ideation, *HS* highly significant

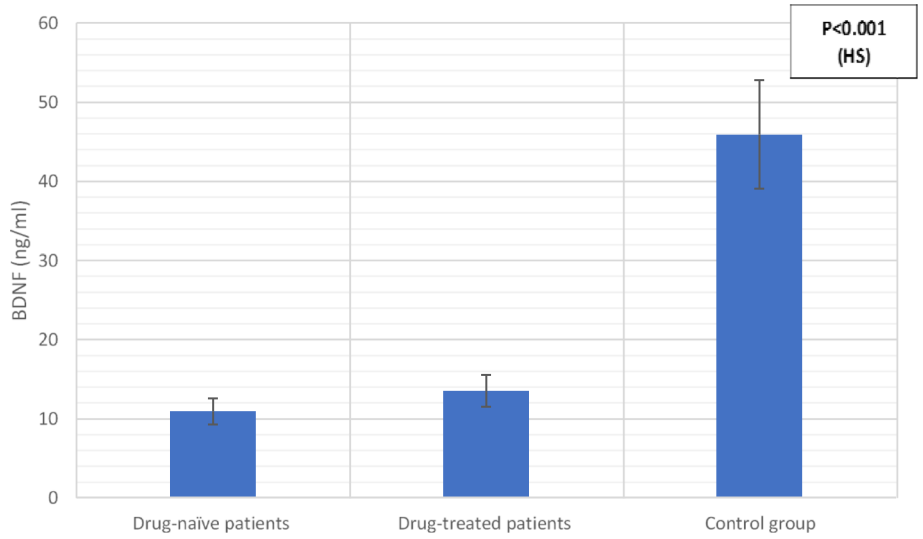

Fig. 1 Serum level of brain-derived neurotrophic factor (BDNF) in the studied groups. HS highly significant

Table 3 Association between BDNF and characteristics of the MDD group

Variables	BDNF (ng/ml)		P	HDRS total score		P
	Median	Range		Median	Range	
Sex						
Males	13.7	12.6–13.9	0.04	16	15–28	0.04
Females	12.9	4.3–13.3	S	17	11–29	S
Marital status						
Married	12.6	4.3–13.9	0.1	25	15–29	*0.001
Not married	13.7	13.3–13.9		16	11–19	HS
Education						
Illiterate, elementary	13.7	11.0–13.9	0.08	16	11–25	0.001
Preparatory, secondary	12.9	11.5–13.9		19	16–27	S
High education	12.8	4.3–13.7		21	16–29	
Occupation						
Working	12.9	12.6–13.9	0.09	19	15–28	0.5
Not working	12.9	4.3–13.9		16	11–29	
Family history						
Positive	12.9	4.3–13.9	0.04	16	11–29	*0.001
Negative	13.2	11.0–13.7	S	21	19–28	HS
Compliance with treatment						
Yes	13.7	12.6–13.9	0.04	16	11–29	*0.001
No	12.9	4.3–13.3	S	22	19–28	H.S.
Suicidal ideation						
BSS < 24	13.7	13.6–13.7	*0.001	16	11–29	*0.001
BSS ≥24	11.0	4.3–11.5	HS	22	19–28	HS
Subgroups						
Drug-naïve patients	12.6	4.3–13.7	*0.001	25	11–29	< 0.001
Drug-treated patients	13.7	12.6–13.9	HS	16	11–28	(HS)

BDNF serum level of brain-derived neurotrophic factor, *HDRS* Hamilton Depression Rating Scale, *BSS* Beck Scale for Suicidal Ideation, *S* significant, *HS* highly significant

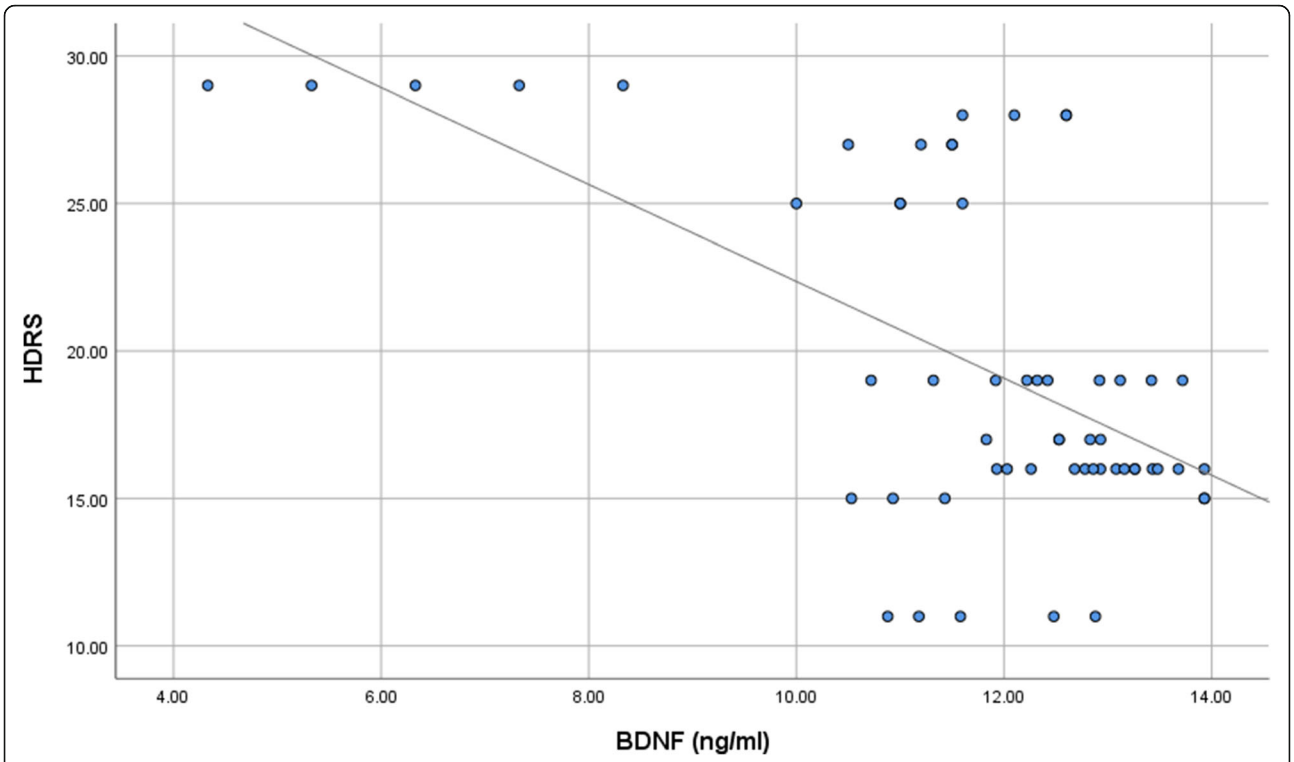

Fig. 2 Correlation between serum level of brain-derived neurotrophic factor (BDNF) and Hamilton Depression Rating Scale (HDRS)

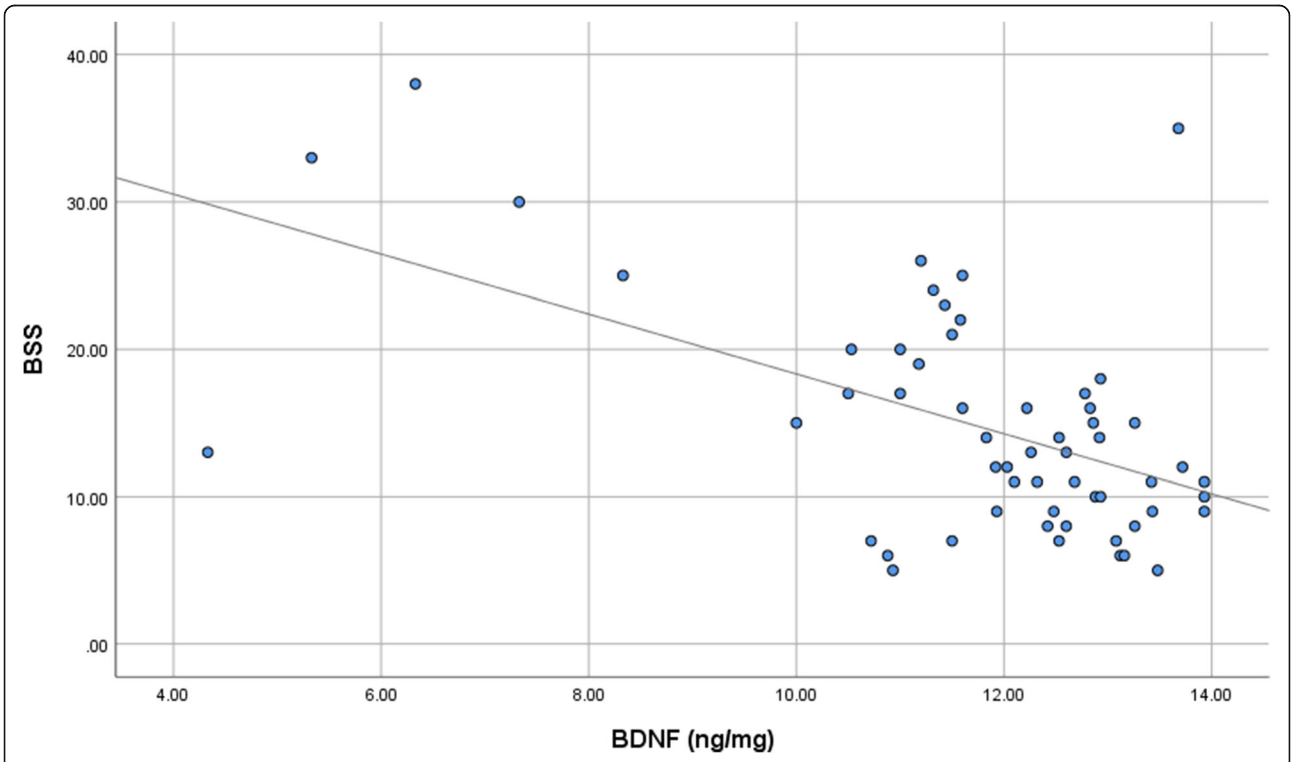

Fig. 3 Correlation between serum level of brain-derived neurotrophic factor (BDNF) and Beck Scale for Suicidal Ideation (BSS)

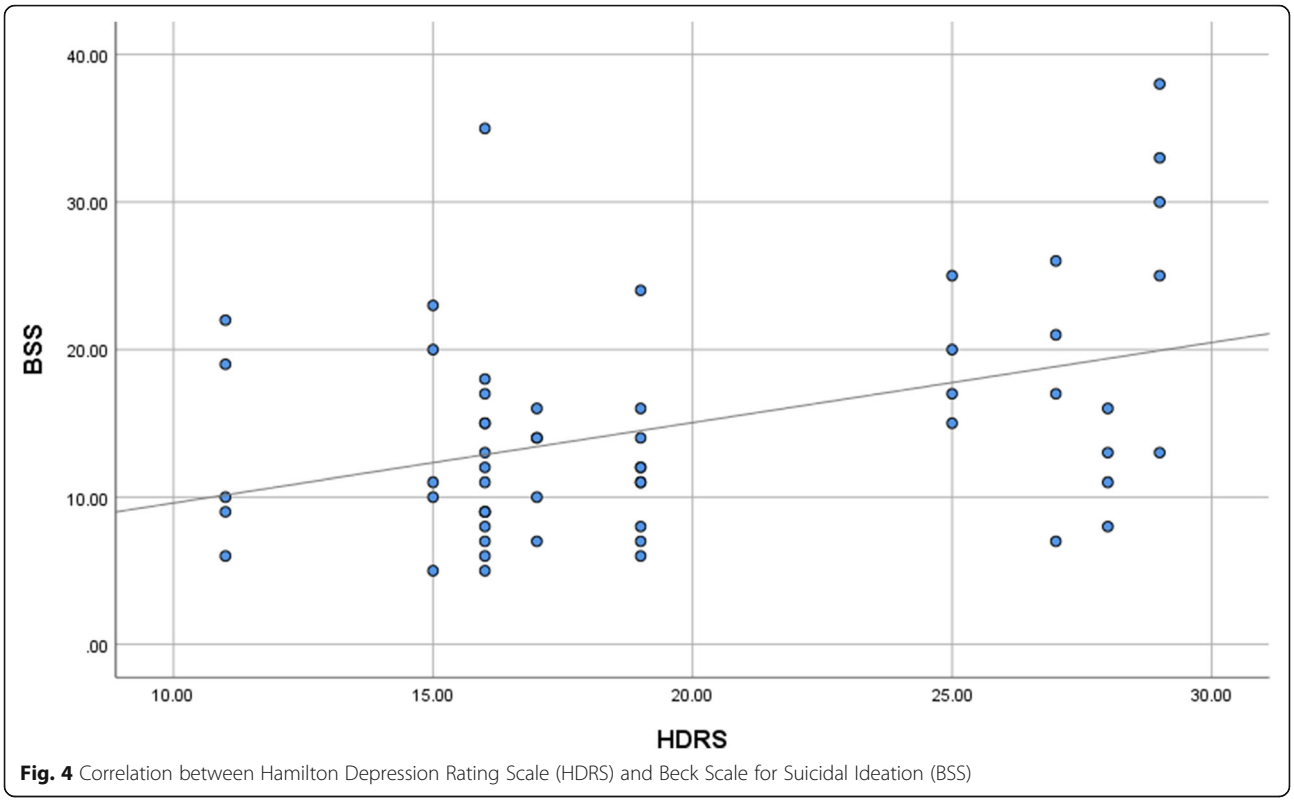

Fig. 4 Correlation between Hamilton Depression Rating Scale (HDRS) and Beck Scale for Suicidal Ideation (BSS)

Discussion

Although major depressive disorder (MDD) and suicide are two significant health problems, their pathophysiology is unclear. Although several studies have been conducted to develop biomarkers for their diagnosis, no diagnostic biomarkers are now widely employed in clinical practice for diagnosing either of them.

There are different types of biomarkers which include diagnostic, predictive, prognostic, and therapeutic response. Diagnostic biomarkers can be used to diagnose disease earlier and predict its occurrence in the future using non-invasive approaches. Patients who are likely to benefit from medication can be identified using predictive biomarkers. Prognostic biomarkers give insight into the course and fate of an illness. Biomarkers of treatment response provide insight into the effect of the therapeutic intervention [32]. As a result of the increased potential for biomarkers, numerous bodily fluids have been studied, including urine, plasma, and CSF. Blood, for example, is easy to obtain and requires minimal invasiveness. MacDonald and his colleague, in his study, documented nine diagnostic biomarkers for MDD; some of them are upregulated like glutamate and alanine, while others are downregulated as Myo-inositol, GABA, phenylalanine, creatine, methionine, oleic acid, and tryptophan [33]. A recent study has used metabolomic technique to identify plasma metabolites that could differentiate MDD patients from healthy subjects,

Table 4 Correlation between BDNF, HDRS, BSS, and other variables in the MDD group

Variables	BDNF		HDRS		BSS	
	r	P	r	P	r	P
Age	0.27	0.04(S)	−0.48	˂0.001(HS)	−0.08	0.6
Education level	−0.16	0.2	0.31	0.02(S)	−0.15	0.3
Age of onset	−0.27	0.04(S)	−0.06	0.7	−0.05	0.7
Disease duration	0.27	0.04(S)	−0.34	0.01(S)	−0.02	0.9
Duration of current episode	0.27	0.04(S)	−0.19	0.2	−0.14	0.3
Number of previous episodes	0.32	0.01(S)	0.03	0.8	0.10	0.5

BDNF serum level of brain-derived neurotrophic factor, *HDRS* Hamilton Depression Rating Scale, *BSS* Beck Scale for Suicidal Ideation, *S* significant, *HS* highly significant

Table 5 Multiple linear regression analysis of HDRS with BDNF and related clinical characteristics

Variables	B	95% CI	S.E.	t	Sig.
Constant	38.9	33.6 – 44.1	2.6	14.8	*0.001 (HS)
BDNF	−1.4	−1.8 to −0.97	0.21	6.7	*0.001 (HS)
Drug-naïve patients	2.0	−0.41–4.5	1.2	1.7	0.1
Disease duration	−0.21	−0.39 to −0.02	0.09	2.3	0.03 (S)
Model summary	F	Dubrin–Watson	R	R^2	Sig.
	20.7	1.6	0.74	0.54	*0.001 (HS)

BDNF serum level of brain-derived neurotrophic factor, *S* significant, *HS* highly significant

investigate the biomarkers in the tryptophan-kynurenine pathway, and find that kynurenic acid (KYNA) may be implicated in the pathophysiology of depression [32].

These studies, as many other studies, were conducted aiming to find specific biomarkers that could make the early diagnosis of depression available, and at the same time accurate, which not only would be very helpful to the early treatment for depression but also will help in other devastating diseases in which depression could be considered as risk factor like neurodegenerative diseases including dementia [34]. Moreover, depression is regarded as a significant complication of many conditions, for example, post-stroke depression (PSD) which may occur within few days and up to 84% at 3 months following stroke with significant impact on its prognosis as it may increase the risk of adverse complications even death [35].

Based on that, we conducted our study to shed light on a potential biomarker for diagnosing MDD patients and assessing the therapeutic response of antidepressant medications in those patients with suicidal ideation (SI). We investigated BDNF as an essential neurotrophic protein which is the most prevalent neurotrophin associated with depression through its involvement in the neurogenesis and neuroplasticity processes [36]. Many studies demonstrated a causative association between entorhinal–hippocampal circuitry and neurogenesis and phenotypes of depression and strongly suggest that the hippocampal circuitry could involve the cerebral cortex in neurogenesis, thereby generating a neural circuitry–neurogenesis model may be a viable concept for combating memory, cognitive deficits, and mood disturbance, which are all associated with depression [37]. Recent research utilizing advanced technologies like optogenetics, chemogenetics, and molecular-based methods has emphasized the entorhinal–hippocampal circuitry's role in controlling neurogenesis and hippocampal-dependent cognitive and affective processes [38]. There is specific activation of entorhinal glutamatergic afferents that improve behaviors associated with depression. According to the preceding studies, impaired neuroplasticity is associated with aberrant neurogenesis, axon branching, dendrites, and synapses. Neuroplasticity abnormalities may be related to variations in the amounts of neurotrophic factors, particularly BDNF, which plays a critical role in neuroplasticity. BDNF production and secretion are activity-dependent, a property associated with neural plasticity [36].

According to the present study, there was a highly statistically significant difference between the study groups in BDNF. Both MDD groups had lower BDNF than the control group, which was consistent with the results from previous studies [39–45].

In MDD subgroups, drug-naïve patients had significantly lower BDNF than drug-treated patients. This result was compatible with Aydemir and colleagues, who reported that treatment of depression improves the serum BDNF level [22]. Besides, Ristevska and colleagues investigated the BDNF levels in untreated depressive patients, which were lower than healthy controls, and the lower levels of BDNF had increased after antidepressant treatment [46]. These findings may postulate that low levels of serum BDNF are a state abnormality that is present during the depression and becomes normal during remission.

In contrast to the present study, Bus and colleagues and Chiou and Huang concluded that maintaining or discontinuing the antidepressant medications was not related to BDNF change [45, 47]. These results imply not only that BDNF contributes to depression but also that depression can lead to BDNF deficiency.

In the present study, a statistically significant difference between the drug-treated MDD patients and the control group was consistent with Molendijk and colleagues [42].

However, Emon and colleagues and Kim and colleagues reported no significant difference in the BDNF levels when comparing drug-treated MDD patients to a control group [48, 49].

In contrast to our study, a recent study by Bilgiç and colleagues found that the mean serum BDNF levels were significantly higher in treatment-free adolescents with MDD than in control subjects [50].

Moreover, Polyakova and colleagues identified that serum BDNF might be regarded as a biomarker for the successful treatment of MDD [51].

Treatment options for depression include pharmaceutical and non-pharmacological interventions such as psychotherapy, electroconvulsive therapy (ECT), and transcranial magnetic stimulation (TMS). Psychotherapy has been shown to have beneficial effects on depression, including the reduction of depressive symptoms and an improvement in quality of life [52].

The involvement of neurotrophins in the mode of action of antidepressant drugs is considerably more obvious than their involvement in depression [36].

Numerous studies reinforce the notion that neurotrophic factors stimulate neural plasticity, enhancing antidepressant responses in MDD patients [53–55]. In their recent review article, Yang and colleagues [36] documented that antidepressants affect neural plasticity on several levels. For example, prolonged antidepressant and acute ketamine therapy improve synaptogenesis and synaptic potency; in addition, ketamine's actions are dependent on BDNF. Moreover, antidepressants may be used to detect increased neurogenesis in the dentate gyrus, which is dependent on BDNF signaling. Finally, antidepressants promote axon growth and dendritic branching and also the production of plasticity-related proteins. Although many specifics concerning whether this is mediated by BDNF or TrkB signaling remain unknown, it is known that BDNF influences both axonal and dendritic growth. These findings indicate a significant association between neuroplasticity and antidepressant effect mode of action, which implies that the impact of plasticity is conveyed, at least in part, by the BDNF signal [36]. On the other hand, in a recent systematic review assessing the impact of psychotherapy on the levels of BDNF in patients with psychiatric disorders, they found a small amount of research examining the impact of psychotherapies on BDNF and concluded that patients who had only psychotherapy had no rise in BDNF levels; however, those who received concomitant medications had a much greater rise compared to those who had only pharmacological treatment [56].

BDNF was associated with some demographic characteristics of MDD patients like age, sex, family history, and disease duration in the present study. It is unknown either the lower levels of BDNF in patients with MDD patients are primary or secondary. One theory is that decreased BDNF levels in patients with depression may represent a genetic susceptibility. Another possibility is that stress-induced BDNF deficiency results in neuronal injury, which results in acquired biological susceptibility [39].

De Azevedo and colleagues concluded that BDNF was positively associated with disease duration, which was found in the present study [43].

One of the critical findings of this study is the significant relation between serum levels of BDNF and the severity of MDD as a significant negative correlation was found between serum BDNF and HAMD scores. These results are in line with much-related research [39, 41, 48].

On the other hand, studies of Chiou and Huang, Ai and colleagues, and Bilgiç and colleagues showed no significant correlation between BDNF and HAMD scores [19, 45, 50].

Regarding suicide ideation in the present study, high BSS (≥24) was associated with low BDNF in MDD patients. We found a statistically significant negative correlation between BDNF and BSS. Deveci and colleagues reported similar results, as well as Kim and colleagues, Lee and colleagues, Chiou and Huang, and Ai and colleagues [19, 40, 45, 49, 57]. However, Bilgiç and colleagues found no correlations between the levels of serum neurotrophins and suicidality [50].

Pathological alterations in BDNF expression are thought to be responsible for cognitive impairments associated with suicide. In mice treated to different stress techniques, a decreased BDNF level was seen in both bodily fluids and brain structures [58]. Similarly, clinical investigations have indicated that patients with MDD and exhibiting suicidal behavior had decreased serum or plasma BDNF concentrations [59]. Postmortem examinations of completed suicides reveal lower BDNF levels in the hippocampus and prefrontal cortex but no alterations in the entorhinal cortex or amygdala. It is worth mentioned that patients who had experienced early childhood trauma and/or committed suicide had reduced BDNF levels in the anterior cingulate cortex than no suicidal subjects with no reported childhood trauma [60].

The current research had certain limitations: First, we examined blood BDNF levels, and the difference between peripheral levels and brain levels of BDNF is controversial [61]. Second, our findings are based on just one measurement of the level of BDNF and at a one-time point besides the relatively small sample size of our sample, so we suggest conducting a more extensive cohort study with a larger sample size and more blood BDNF measurements which would strengthen the findings. Finally, there are various other essential variables like genetic polymorphisms and epigenetics that influence BDNF levels. Unfortunately, we were not able to investigate any of them.

Conclusion

These findings extend the neurotrophic concept of depression by identifying the decreased BDNF levels as a peripheral biomarker of MDD. Our assessment of depression and suicidal ideation (SI) and their relationship to decreased BDNF levels shed light on the etiopathology of MDD and its related suicidality and should be more studied to understand better the mechanisms by which they develop. To further explore the effect of BDNF in suicide, larger study sizes and a range of psychiatric diagnoses associated with suicide attempts are required.

Abbreviations

BDNF: Brain-derived neurotrophic factor; MDD: Major depressive disorder; SCID: Structured Clinical Interview for DSM-5; HDRS: Hamilton Depression Rating Scale; BSS: Beck Scale for Suicidal Ideation; WHO: World Health Organization; TrkB: Tropomyosin-related tyrosine kinases; mRNA: Messenger ribonucleic acid; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; SI: Suicidal ideation; MAPK: Mitogen-activated protein kinase; SNPs: Single-nucleotide polymorphisms; Val66Met: Methionine (Met) substitution for valine (Val) at codon 66; *5-HTTLPR*: Serotonin transporter-

linked polymorphic region; 5-HTT: 5-Hydroxytryptamine transporter; DNA: Deoxyribonucleic acid; GABA: Gamma aminobutyric acid; KYNA: Kynurenic acid; PSD: Post-stroke depression

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Authors' contributions
AMY, AEM, and GMS designed the work and applied the psychometric assessment and shared data collection. ASI shared in collecting the data. AMY, AEM, GMS, and ASI interviewed the participants for diagnosing the psychiatric disorders if present. All authors contributed to the conception, preparation, and writing of this article. AMY gave the paper a final review and then forwarded the report for publication. All authors have read and approved the final manuscript.

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Declarations

Ethics approval and consent to participate
Approval of the Institutional Review Board (IRB) of Zagazig University, Faculty of Medicine, was obtained after revising the study protocol (ZU-IRB#2021). The participants were knowledgeable about the nature, methods, and aim of the study, and the researchers had written consent from all the participants. All participant's data were confidential.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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References

1. Depression WH. Other common mental disorders: global health estimates. Geneva: World Health Organization; 2017. p. 1–24.
2. Saveanu RV, Nemeroff CB. Etiology of depression: genetic and environmental factors. Psychiatr Clin. 2012;35(1):51–71.
3. Slavich GM. Deconstructing depression: a diathesis-stress perspective. APS Observer. 2004;17(9):15–21.
4. Wray NR, Ripke S, Mattheisen M, Trzaskowski M, Byrne EM, Abdellaoui A. Major Depressive Disorder Working. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. Nat Genet. 2018;50(5):668.
5. Howard DM, Adams MJ, Clarke TK, Hafferty JD, Gibson J, Shirali M, et al. Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. Nat Neurosci. 2019;22(3):343–52. https://doi.org/10.1038/s41593-018-0326-7.
6. Krishnan V, Nestler EJ. The molecular neurobiology of depression. Nature. 2008;455(7215):894–902. https://doi.org/10.1038/nature07455.
7. Hindmarch I. Beyond the monoamine hypothesis: mechanisms, molecules and methods. Eur Psychiatry. 2002;17:294–9.
8. Duman RS, Heninger GR, Nestler EJ. A molecular and cellular theory of depression. Arch Gen Psychiatry. 1997;54(7):597–606. https://doi.org/10.1001/archpsyc.1997.01830190015002.
9. Saarelainen T, Hendolin P, Lucas G, Koponen E, Sairanen M, MacDonald E, et al. Activation of the TrkB neurotrophin receptor is induced by antidepressant drugs and is required for antidepressant-induced behavioral effects. J Neurosci. 2003;23(1):349–57. https://doi.org/10.1523/JNEUROSCI.23-01-00349.2003.
10. Duman RS, Monteggia LM. A neurotrophic model for stress-related mood disorders. Biol Psychiatry. 2006;59(12):1116–27. https://doi.org/10.1016/j.biopsych.2006.02.013.
11. Phillips C. Brain-derived neurotrophic factor, depression, and physical activity: making the neuroplastic connection. Neural Plast. 2017;2017:1–17. https://doi.org/10.1155/2017/7260130.
12. Rosso P, De Nicolò S, Carito V, Fiore M, Iannitelli A, Moreno S, et al. Ocular nerve growth factor administration modulates brain-derived neurotrophic factor signaling in prefrontal cortex of healthy and diabetic rats. CNS Neurosci Ther. 2017;23(3):198–208. https://doi.org/10.1111/cns.12661.
13. Gyekis JP, Yu W, Dong S, Wang H, Qian J, Kota P, et al. No association of genetic variants in BDNF with major depression: a meta-and gene-based analysis. Am J Med Genet Part B. 2013;162(1):61–70. https://doi.org/10.1002/ajmg.b.32122.
14. Bleys D, Luyten P, Soenens B, Claes S. Gene-environment interactions between stress and 5-HTTLPR in depression: a meta-analytic update. J Affect Disord. 2018;226:339–45. https://doi.org/10.1016/j.jad.2017.09.050.
15. Martinowich K, Lu B. Interaction between BDNF and serotonin: role in mood disorders. NPP. 2008;33(1):73–83.
16. Schröter K, Brum M, Brunkhorst-Kanaan N, Tole F, Ziegler C, Domschke K, et al. Longitudinal multi-level biomarker analysis of BDNF in major depression and bipolar disorder. Eur Arch Psychiatry Clin Neurosci. 2020;270:169–81 [PubMed] [CrossRef] [Google Scholar].
17. Hsieh MT, Lin CC, Lee CT, Huang TL. Abnormal brain-derived neurotrophic factor exon IX promoter methylation, protein, and mRNA levels in patients with major depressive disorder. J Clin Med. 2019;8:568 [PMC free article] [PubMed] [CrossRef] [Google Scholar].
18. Lin CC, Hung YY, Tsai MC, Huang TL. Increased serum brain-derived neurotrophic factor in male schizophrenic patients with metabolic syndrome. Med. 2017;96:e7089 [PMC free article] [PubMed] [CrossRef] [Google Scholar].
19. Ai M, Wang J, Chen J, Wang W, Xu X, Gan Y, et al. Plasma brain-derived neurotrophic factor (BDNF) concentration and the *BDNF* Val66Met polymorphism in suicide: a prospective study in patients with depressive disorder. Pharmacogenom Personalized Med. 2019;12:97–106 [PMC free article] [PubMed] [CrossRef] [Google Scholar].
20. Jain KK. Applications of biotechnology in neurology. Heidelberg: Springer Science. J Media Bu Stud. 2013. https://doi.org/10.1007/978-1-62703-272-8.
21. Wootton BM, Worden BL, Norberg MM, Grisham JR, Steketee G. A clinician's quick guide to evidence-based approaches: hoarding disorder. J Clin Psychol. 2019;23(1):85–7. https://doi.org/10.1111/cp.12176.
22. Aydemir O, Deveci A, Taneli F. The effect of chronic antidepressant treatment on serum brain-derived neurotrophic factor levels in depressed patients: a preliminary study. Prog Neuropsychopharmacol Biol Psychiatry. 2005;29(2):261–5. Epub 2004. PMID: 15694233.
23. Dean AG, Sullivan KM, Soe MM. OpenEpi: open source epidemiologic statistics for public health, version. 2013.
24. Osório FL, Loureiro SR, Hallak JE, Machado-de-Sousa JP, Ushirohira JM, Baes CV, et al. Clinical validity and intrarater and test-retest reliability of the Structured Clinical Interview for DSM-5–Clinician Version (SCID-5-CV). Psychiatry Clin Neurosci. 2019;73(12):754–60. https://doi.org/10.1111/pcn.12931.
25. Bachner YG. Psychometric properties of responses to an Arabic version of the Hamilton Depression Rating Scale (HAM-D6). JAPNA. 2016;22(1):27–30. https://doi.org/10.1177/1078390316629959.
26. Beck AT, Steer RA, Ranieri WF. Scale for suicide ideation: psychometric properties of a self-report version. J Clin Psychol. 1988;44(4):499–505. https://doi.org/10.1002/1097-4679(198807)44:4<499::AID-JCLP2270440404>3.0.CO;2-6.
27. Cochrane-Brink KA, Lofchy JS, Sakinofsky I. Clinical rating scales in suicide risk assessment. Gen Hosp Psychiatry. 2000;22(6):445–51. https://doi.org/10.1016/S0163-8343(00)00106-7.
28. Alsalman R. Gender differences in suicide ideation among college students in Kuwait. Eur Psychiatry. 2016;33(S1):S597–6.
29. Sista R, Hua Z, Thwar P, Sudarsan A, Srinivasan V, Eckhardt A, et al. Development of a digital microfluidic platform for point of care testing. Lab Chip. 2008;8(12):2091–104. https://doi.org/10.1039/b814922d.
30. Spss I. IBM SPSS Statistics for Windows, version 25. Armonk: IBM SPSS Corp. [Google Scholar]; 2017.
31. Turner P. Critical values for the Durbin-Watson test in large samples. Appl Econ Lett. 2020;27(18):1495–9. https://doi.org/10.1080/13504851.2019.1691711.
32. Erabi H, Okada G, Shibasaki C, Setoyama D, Kang D, Takamura M, et al. Kynurenic acid is a potential overlapped biomarker between diagnosis and treatment response for depression from metabolome analysis. Sci Rep. 2020;10(1):1–8.

33. MacDonald K, Krishnan A, Cervenka E, Hu G, Guadagno E, Trakadis Y. Biomarkers for major depressive and bipolar disorders using metabolomics: a systematic review. AJMG: B. 2019;180(2):122–37.
34. Cantón-Habas V, Rich-Ruiz M, Romero-Saldaña M, Carrera-González MP. Depression as a risk factor for dementia and Alzheimer's disease. Biomedicines. 2020;8(11):457.
35. Kowalska K, Krzywoszański Ł, Droś J, Pasińska P, Wilk A, Klimkowicz-Mrowiec A. Early depression independently of other neuropsychiatric conditions, influences disability and mortality after stroke (research study—part of PROPOLIS Study). Biomedicines. 2020;8(11):509. https://doi.org/10.3390/biomedicines8110509.
36. Yang T, Nie Z, Shu H, Kuang Y, Chen X, Cheng J, et al. The role of BDNF on neural plasticity in depression. Front Cell Neurosci. 2020;14:82. https://doi.org/10.3389/fncel.2020.00082.
37. Luna VM, Anacker C, Burghardt NS, Khandaker H, Andreu V, Millette A, et al. Adult-born hippocampal neurons bidirectionally modulate entorhinal inputs into the dentate gyrus. Science. 2019;364(6440):578–83. https://doi.org/10.1126/science.aat8789.
38. Kim IB, Park S-C. Neural circuitry–neurogenesis coupling model of depression. Int J Mol Sci. 2021;22(5):2468. https://doi.org/10.3390/ijms22052468.
39. Shimizu E, Hashimoto K, Okamura N, Koike K, Komatsu N, Kumakiri C, et al. Alterations of serum levels of brain-derived neurotrophic factor (BDNF) in depressed patients with or without antidepressants. Biol Psychiatry. 2003;54(1):70–5. https://doi.org/10.1016/S0006-3223(03)00181-1.
40. Lee BH, Kim H, Park SH, Kim YK. Decreased plasma BDNF level in depressive patients. J Affect Disord. 2007;101(1-3):239–44. https://doi.org/10.1016/j.jad.2006.11.005.
41. Satomura E, Baba H, Nakano Y, Maeshima H, Suzuki T, Arai H. Correlations between brain-derived neurotrophic factor and clinical symptoms in medicated patients with major depression. J Affect Disord. 2011;135(1-3):332–5. https://doi.org/10.1016/j.jad.2011.06.041.
42. Molendijk ML, Bus BA, Spinhoven P, Penninx BW, Kenis G, Prickaerts J, et al. Serum levels of brain-derived neurotrophic factor in major depressive disorder: state–trait issues, clinical features and pharmacological treatment. J Mol Psychiatry. 2011;16(11):1088–95. https://doi.org/10.1038/mp.2010.98.
43. de Azevedo CT, Mondin TC, Wiener CD, Marques MB, de Avila FB, Pinheiro RT, et al. Neurotrophic factors, clinical features and gender differences in depression. Neurochem Res. 2014;39(8):1571–8.
44. Ladea M, Bran M. Brain derived neurotrophic factor (BDNF) levels in depressed women treated with open-label escitalopram. Psychiatr Danub. 2013;25(2):0–132.
45. Chiou YJ, Huang TL. Serum brain-derived neurotrophic factors in Taiwanese patients with drug-naive first-episode major depressive disorder: effects of antidepressants. Int J Neuropsychopharmacol. 2017;20(3):213–8.
46. Ristevska-Dimitrovska G, Shishkov R, Pejoska Gerazova V, Vujovik V, Stefanovski B, Novotni A, et al. Different serum BDNF levels in depression: results from BDNF studies in FYR Macedonia and Bulgaria. Psychiatr Danub. 2013;25(2):0–127.
47. Bus BA, Molendijk ML, Tendolkar I, Penninx BW, Prickaerts J, Elzinga BM, et al. Chronic depression is associated with a pronounced decrease in serum brain-derived neurotrophic factor over time. Mol Psychiatry. 2015;20(5):602–8. https://doi.org/10.1038/mp.2014.83.
48. Emon MP, Das R, Nishuty NL, Qusar MS, Bhuiyan MA, Islam MR. Reduced serum BDNF levels are associated with the increased risk for developing MDD: a case–control study with or without antidepressant therapy. BMC Res Notes. 2020;13(1):1–6.
49. Kim JM, Stewart R, Kim SW, Yang SJ, Shin IS, Kim YH, et al. Interactions between life stressors and susceptibility genes (5-HTTLPR and BDNF) on depression in Korean elders. Biol Psychiatry. 2007;62(5):423–8. https://doi.org/10.1016/j.biopsych.2006.11.020.
50. Bilgiç A, Çelikkol Sadıç Ç, Kılınç İ, Akça ÖF. Exploring the association between depression, suicidality and serum neurotrophin levels in adolescents. Int J Psychiatry Clin Pract. 2020;24(2):143–50. https://doi.org/10.1080/13651501.2020.1723643.
51. Polyakova M, Stuke K, Schuemberg K, Mueller K, Schoenknecht P, Schroeter ML. BDNF as a biomarker for successful treatment of mood disorders: a systematic, quantitative meta-analysis. J Affect Disord. 2015;174:432–40. https://doi.org/10.1016/j.jad.2014.11.044.
52. Balogh L, Tanaka M, Török N, Vécsei L, Taguchi S. Crosstalk between existential phenomenological psychotherapy and neurological sciences in mood and anxiety disorders. Biomedicines. 2021;9(4):340. https://doi.org/10.3390/biomedicines9040340.
53. Nestler EJ, Barrot M, DiLeone RJ, Eisch AJ, Gold SJ, Monteggia LM. Neurobiology of depression. Neuron. 2002;34(1):13–25. https://doi.org/10.1016/S0896-6273(02)00653-0.
54. Castrén E, Hen R. Neuronal plasticity and antidepressant actions. Trends Neurosci. 2013;36(5):259–67. https://doi.org/10.1016/j.tins.2012.12.010.
55. Castrén E, Kojima M. Brain-derived neurotrophic factor in mood disorders and antidepressant treatments. Neurobiol Dis. 2017;97:119–26.
56. Claudino FCA, Gonçalves L, Schuch FB, Martins HRS, da Rocha NS. The effects of individual psychotherapy in BDNF levels of patients with mental disorders: a systematic review. Fpsyt. 2020;11:445.
57. Deveci A, Aydemir O, Taskin O, Taneli F, Esen-Danaci A. Serum BDNF levels in suicide attempters related to psychosocial stressors: a comparative study with depression. Neuropsychobiology. 2007;56(2-3):93–7. https://doi.org/10.1159/000111539.
58. Nakagawa Y, To M, Saruta J, Yamamoto Y, Yamamoto T, Shimizu T, et al. Effect of social isolation stress on saliva BDNF in rat. J Oral Sci. 2019;61(4):516–20. https://doi.org/10.2334/josnusd.18-0409.
59. Eisen RB, Perera S, Banfield L, Anglin R, Minuzzi L, Samaan Z. Association between BDNF levels and suicidal behaviour: a systematic review and meta-analysis. Syst Rev. 2015;4(1):187. https://doi.org/10.1186/s13643-015-0179-z.
60. Misztak P, Pańczyszyn-Trzewik P, Nowak G, Sowa-Kućma M. Epigenetic marks and their relationship with BDNF in the brain of suicide victims. PLoS One. 2020;15(9):e0239335. https://doi.org/10.1371/journal.pone.0239335.
61. Salas-Magaña M, Tovilla-Zárate CA, González-Castro TB, Juárez-Rojop IE, López-Narváez ML, Rodríguez-Pérez JM, et al. Decrease in brain-derived neurotrophic factor at plasma level but not in serum concentrations in suicide behavior: a systematic review and meta-analysis. Brain Behav. 2017;7(6):e00706. https://doi.org/10.1002/brb3.706.

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