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Serum BDNF: A Potential Biomarker for Major Depressive Disorder and Antidepressant Response Prediction

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Abstract

Background: The neurotrophin hypothesis of depression emphasizes the role of down-regulation of Brain-derived Neurotrophic Factor (BDNF) in the pathophysiology of Major Depressive Disorder (MDD). Patients with MDD may have reduced serum BDNF levels and treatment with antidepressants may stimulate the expression of BDNF resulting in normalization of BDNF after successful treatment.

Objective: To determine whether serum BDNF in MDD patients is lower than in healthy control (HC) subjects, whether all MDD patients show lower than normal levels and whether MDD patients with comparatively higher BDNF levels will respond better to antidepressant therapy.

Method: Ninety medically healthy outpatients diagnosed with MDD were enrolled in one of two studies. In Study-1 patients were treated with escitalopram and in Study-2 with quetiapine. The main outcome measure was the 17-item Hamilton Depression Scale (HAM-D) scores. Of the 90 enrolled patients 54 had baseline BDNF values. Thirteen HC subjects for whom serum BDNF values were available were included for comparison.

Results: Mean baseline serum BDNF did not differ between MDD and HC subjects. When the median BDNF value was used as a "cut score" to subdivide the MDD group into an above median (high) and a below median (low) subgroup, significant differences emerged. Both subgroups differed significantly from the HC mean and from each other. Depressive episodes of greater than 6 months' duration correlated significantly with higher BDNF levels (p=0.03). Higher BDNF levels predicted a high probability of a positive treatment response (p=0.02) to either of the two pharmacologic agents used.

Conclusions: Serum BDNF levels can be higher or lower in MDD subjects when compared to healthy controls. A high baseline BDNF level may predict a positive treatment response to antidepressant drug therapy, suggesting a possible future role of serum BDNF level as a useful biomarker for subtyping MDD and predicting antidepressant treatment response.

Keywords: Major depressive disorder; Brain-derived neurotrophic factor antidepressant response; Escitalopram; Quetiapin

Introduction

Brain-derived Neurotrophic Factor (BDNF) is a member of the neurotrophin family of growth factors. This is a class of homo-dimeric proteins that is densely distributed throughout the brain and a variety of peripheral tissues. BDNF participates in the regulation of synaptic structure and neurotransmitter release [1-4] and is crucial for the viability of neurons in those brain circuits that regulate emotion, memory, learning, sleep and appetite [5,6]. It plays a critical role in the regulation of activity-dependent plasticity mechanisms, such as long-term potentiation (LTP), learning, and long-term memory (LTM) in the synaptic regions of hippocampal neurons [1,2,5]. BDNF promotes cellular differentiation, neuronal survival and repair from injury in the adult nervous system and is involved in the regulation of apoptosis, outgrowth of select neurons both in the peripheral and central nervous system (CNS) during development as well as adulthood [7,8]. BDNF-mediated neuroadaptive changes in pre-frontal and hippocampal circuits have been implicated in the pathogenesis of depressive mood disorders and antidepressant drug action [9].

Recent preclinical, clinical and genetic studies have focused largely on BDNF mediated neuroadaptive changes in the pathogenesis of major depression. The neurotrophin hypothesis of depression postulates stress-induced down-regulation of BDNF mRNA expression in the hippocampus and pre-frontal cortex, resultant cell loss, and neuronal atrophy as the key mechanism involved in the pathophysiology of MDD [10,11]. Deficient neurotrophin-mediated synaptic plasticity enhances susceptibility to environmental challenges that contribute to, if not ultimately lead to, the pathophysiology of depression, and other stress-related psychiatric illnesses [5,11,12]. Genetic studies have also associated polymorphisms in the BDNF gene with depression-related traits, and family-based association studies

have identified the BDNF gene as a major risk locus for mood cycling in bipolar disorder [11,13-16].

Of note, BDNF is most abundantly expressed in the hippocampus and cerebral cortex, as well as a variety of peripheral tissues, for example, visceral epithelial cells, vascular endothelial cells, immune cells and platelets as a site of storage and release, but not synthesis. All of these have been identified as sources contributing to serum BDNF levels [15-18]. BDNF crosses the blood-brain-barrier to a minor extent. The functional significance of serum BDNF remains largely unknown, however, a growing body of evidence suggests serum BDNF levels may be decreased in depressed patients and normalized by antidepressants therapies [19-28]. Since pre-clinical studies have indicated that BDNF administered into the blood stream is capable of exerting an antidepressant-like cellular response in the brain [14], and whether or not serum BDNF levels reflect brain BDNF levels [19-24], these findings raise the possibility that serum BDNF levels may be a potentially useful diagnostic biomarker for MDD and antidepressant response.

Method

Aim of study

The aim of this study was to assess serum BDNF levels in a group of patients diagnosed with MDD and compare them to a group of healthy control (HC) subjects. We hypothesized that the MDD group would show heterogeneous distribution of serum BDNF values similar to our earlier reported finding with plasma levels of Vascular Endothelial Growth Factor (VEGF) in depression [27]. Ancillary goals were to explore whether a patient's baseline BDNF serum level could be related to the patient's length of depressive episode, recent use of antidepressants, and subsequent response to antidepressant therapy. In two consecutively run studies two different patient groups were treated either with escitalopram (Study-1) or quetiapine (Study-2) monotherapeutically. The rationale for using the atypical antipsychotic, quetiapine, was based on the fact that a major biologically active metabolite of quetiapine, norquetiapine, is a norepinephrine reuptake inhibitor in contradistinction to escitalopram, a specific serotonin reuptake inhibitor. In this paper we present baseline data from the entire group of MDD subjects who participated in either of the two treatment protocols. Our ultimate goal was to gain a clearer understanding of the potential role of BDNF as a biomarker of MDD.

Study population

This study was approved by the Institutional Review Board of Loyola University Medical Center and was conducted according to the principles in the Declaration of Helsinki. Males and females between 20 and 65 years of age who met DSM-IV criteria for MDD, first episode or recurrent type, who were otherwise physically healthy and mentally capable to give informed consent, were considered as candidates. The MINI Structured Interview was used to establish the psychiatric diagnosis. The current episode had to be of at least 1 month duration and patients could not have had psychopharmacological treatment over the preceding four weeks. Subjects on antidepressant medication who had failed to respond were given a 4–week washout while being closely monitored for possible suicidality or significant worsening of their depression. A minimum score of 18 on their 17-item Hamilton Depression Scale (HAM-D17) was required for study admission. Additional study criteria stipulated

that subjects be free of any active source of inflammation including gum disease. Hypertension, dyslipidemia, diabetes mellitus, history of smoking or substance abuse in the preceding 6 months, and history of heart disease were exclusion criteria. Female subjects could not be pregnant, lactating, or taking oral contraceptives. Since the study stipulated treatment with a psychoactive medication, sexually active female subjects had to agree to practice reliable contraception for the duration of the study.

	MDD Subjects	Healthy Control Subjects	P Value
Study Participants	54	13	
Demographics			
Age (±SD) range	42.1 (12.2) 19-67	35.6 (11.5) 21-54	0.09[a]
BMI (±SD) range	31.3 (6.3) 19.1-51.6	25.2 (4.3) 19.7-34.7	0.002[a]
Female (pre-menopausal)	59.3% (84.4%)	53.8% (100.0%)	0.72[b] (0.26[b])
Caucasian	51.9% (N=28)	61.5% (N=8)	0.23[b]
Non-Caucasian	48.1% (N=26)	38.5% (N=5)	
Hx of Tobacco Use (not current use)	Yes=0	Yes=0	1.00[b]
	No=54	No=13	

[1]Only subjects are included for whom BDNF values were available for analysis

[a]Two-sample t test

[b]Chi-square test

Table 1: Demographics of MDD and HC Subjects.

Screening blood samples (collected post-fasting) were obtained to ensure a healthy status and included a complete blood count, complete metabolic panel, lipid profile, thyroid function, urinalysis and pregnancy test. The presence of any clinically significant abnormalities excluded the prospective participant, leading to non-acceptance into the study and provision of an alternative course of care. The presence of active suicidality and/or other Axis I diagnoses were also exclusion criteria. Ninety MDD patients (N=90) who met the inclusion/exclusion criteria and successfully completed the baseline evaluations were enrolled in one of the two treatment studies and received psychoactive medication for a 12-week treatment phase. Of these 54 had serum samples available for the measurement of BDNF levels; 37 were treated with quetiapine and 17 were treated with escitalopram. Their demographic data is shown in Table 1.

Healthy control subjects

Eligible healthy control (HC) subjects were recruited from the medical center by flyers and word of mouth. They were screened by the same clinician investigators as the MDD subjects after providing written informed consent approved by the Institutional Review Board. Hypertension, dyslipidemia, diabetes mellitus, neurological or autoimmune disorders, history of smoking or substance abuse in the preceding 6 months, and history of heart disease were exclusion criteria. The screening tests included routine laboratory tests, a physical examination, medical history and a psychiatric examination. The psychiatric diagnostic structured interview utilized the Mini International Neuropsychiatric Interview (MINI) and psychiatric

rating scales. HAM-D17 and Beck Depression Inventory (BDI) scores had to be less than 5 to be considered a healthy subject. Main exclusion criteria for HC subjects included any kind of medical, inflammatory or mental illness (substance use, mental illness or substance use amongst first degree relatives), or if they were pregnant or lactating females. If the screening tests fell within normal range, subjects were enrolled and scheduled for the baseline visit soon thereafter. Once deemed eligible, their baseline visit was scheduled. A total of twenty-seven HC subjects were thus enrolled. However, only 13 HC subjects had BDNF values available for statistical analyses. Their demographic data is shown in Table 1.

Study design

Two clinic screening visits (Screening-1, 2) preceded all baseline measurements, a design which conveniently allowed for acclimation to the clinic setting before the experiments began. Screening visit-1 involved collection of blood and urine samples to obtain a complete blood count with differential, complete metabolic panel with electrolytes, thyroid function, lipid profile, hCG pregnancy test and a toxicology screen.

Psychiatric History	
Previously on antidepressants	Yes=64.7% (N=33)
	No=35.3% (N=18)
Previous episode of depression	Yes=85.2% (N=46)
	No=14.8% (N=8)
Current episode length	2 wks- 6 months=31.5% (N=17)
	6 months-1 yr=14.8% (N=8)
	1 yr+=51.9% (N=28)
Family Hx of depressive disorder	Yes=59.6% (N=28)
	No=40.4% (N=19)
Family Hx of other psychiatric disorder	Yes=59.6% (N=28)
	No=40.4% (N=19)
if N <54=information not available	

Table 2: Clinical Characteristics of MDD Subjects.

Screening-2 involved a physical exam, inclusive of a gum exam, followed by a structured diagnostic interview and a battery of structured and mood rating instruments: MINI, Family History Questionnaire, Gynecologic History Questionnaire, Hamilton Rating Scale for Depression (HAM-D) and Anxiety (HAM-A), Beck Depression Inventory (BDI), Beck Scale for Suicide (BSS) and Clinical Global Impression (CGI).

In most cases the actual baseline visit occurred within a day or two after the second screening visit, unless the mandatory four-week antidepressant washout period had to occur first. The clinical characteristics of the MDD patient group are shown in Table 2.

For the baseline visit all subjects (MDD or HC) were instructed to follow standard operating procedures as follows. They were to turn the lights off between 10 and 11 pm on the night preceding the blood draw. They were not allowed to take aspirin (previous 240 hours), antihistamines (previous 72 hours), acetaminophen (previous 72 hours), vitamins C or E (previous 72 hours), sleeping pills (previous 72

hours), caffeinated beverages (8 hours), physical exertion (8 hours) or tobacco products (though none were smokers). They were to have fasted overnight with only water being allowed until after the blood draw. All blood draws were scheduled to occur between 9 and 10 am. Upon arrival at the clinic, the subjects reclined in a quiet air-conditioned room for 20 minutes. A needle was inserted into the antecubital vein and the first 3 ml of blood was discarded to avoid tissue factors released from the site of the venipuncture. After the baseline blood samples were drawn MDD subjects (but not HC subjects) were started on either escitalopram (Study-1) or quetiapine (Study-2). Escitalopram dosing was started at 10 mg/day and maintained in the range of 10–40 mg/day. Quetiapine dosing was started at 25 mg/day and titrated at the discretion of the investigators up to a 300 mg/day. Enrolled patients received no other form of therapy during the study period. Follow-up blood draws and assessments using the aforementioned clinician-rated depression and anxiety scales were performed at weeks 0, 2, 4, 8, 12.

Study patients were required to complete at least 8 weeks of study participation and complete end-of-study assessment to be regarded as study completers. Patients who chose to withdraw from the study on or after 8 weeks of treatment, and completed the battery of final assessment tests, had their last observation carried forward for data analysis (LOCF). Subjects who failed to respond or had intolerable side effects were treated with another antidepressant at the discretion of the investigator.

Measurement of serum BDNF

Blood samples were separated into plasma and serum samples and were immediately stored at –80°C until analyzed. Storage time averaged 28 months. All samples had been coded and were analyzed in a single assay. Laboratory personnel conducting the assay were blinded to the identity of the subject and the nature of the sample analyzed. Values were reported to the principal investigator who decoded them before proceeding with the statistical analyses. Serum BDNF levels in patients and controls were determined using the enzyme-linked immunosorbent assay (ELISA) method. The kit for the determination of BDNF (Human BDNF Quantakine® kit) was obtained from R&D Systems, Inc., Minneapolis, MN. BDNF was measured according to the manufacturer's instructions. The results are expressed as ng of BDNF per ml of serum. Serum samples were not available for all study subjects due to technical difficulties, such as inadequate serum. Of the 90 enrolled MDD subjects 54 samples were available for measurement of serum BDNF and 13 of the 27 HC subjects.

Statistical analyses

The SPSS version 20 was used for the analyses. Prior to conducting tests of statistical significance the distribution of baseline BDNF measurements was examined to ensure that the assumption of normality was not violated. Following this determination, the difference in baseline BDNF values between healthy and MDD subjects was tested with the Student's t test for Independent Samples.

Depressive disorders are known to be heterogeneous disorders and biomarker values display a wide range. Hence when comparisons are made between mean values of an entire patient group with inherent heterogeneity and a healthy control group, not infrequently statistically significant differences fail to emerge. This appeared to be the case in our sample of BDNF values indicating the presence of subgroups within the total study group of MDD subjects. Accordingly,

it was justified to calculate the median value and use it in an exploratory manner to possibly identify two subgroups of MDD patients, one above the median ("high") and one below ("low") (Figure 1). We believe such an approach is legitimate as an initial and exploratory approach to better understand the data and identify possible factors contributing to the variance in the data. To the best of our knowledge, the reviewed literature does not provide a clinically relevant range of normal vs. abnormal serum BDNF levels.
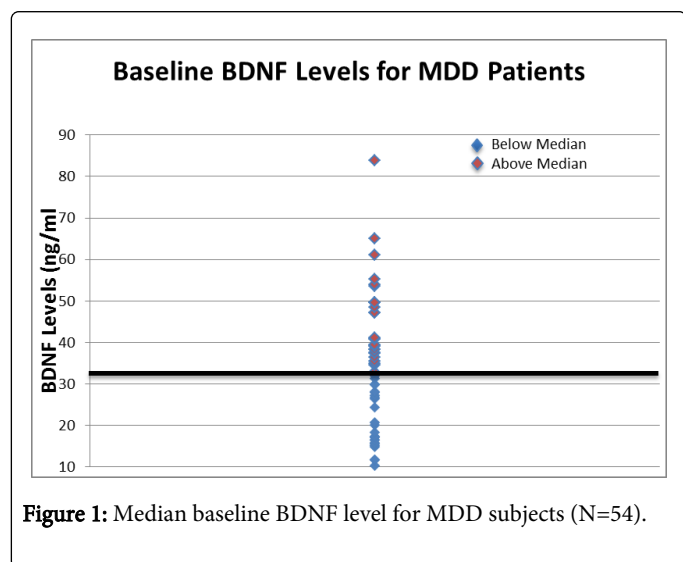

Figure 1: Median baseline BDNF level for MDD subjects (N=54).

In order to identify potential confounding variables such as age, gender, and BMI, the Student t-test was used to make comparisons between the HC group and the MDD group (Table 1). BMI was significantly different between these two groups (p=0.002).

Group	Mean (ng/mL)	SD	P-value
Healthy control vs. ."High" BDNF group N=40	34.66 / 45.57	15.2 / 11.39	0.015
Healthy control vs. "Low" BDNF group N=40	34.66 / 21.8	15.2 / 7.2	0.011
"Low" BDNF group vs. "High" BDNF group N=54	21.8 / 45.57	7.2 / 11.39	<0.005
Levene's test for Equality of Variance and Independent samples t-test for equality of means.			

Table 3: Difference Between the Means of MDD and HC Groups.

The frequencies of clinical characteristics for the MDD group show the majority of subjects to have had a previous episode of depression, to have been on an antidepressant before, and to have a family history of depression or psychiatric disorders (Table 2). Given that the sample size was small in the analyses of some of these variables (e.g., length of treatment, length of the depressive episode) a Bonferroni adjusted p value was used (p=0.0125).

Levene's test for Equality of Variances and Independent Samples t-test were used to determine differences between the healthy control

group and each MDD subgroup, along with the mean differences between the two MDD subgroups (Table 3).

Chi-Squared (χ2) and Fisher Exact Probability tests were used to determine whether "high" or "low" BDNF groups could better predict treatment response in MDD subjects who completed all 12 weeks of the study (Table 4).

Treatment Response	"Low" BDNF	"High" BDNF
Yes	8 (53%)	21 (87%)
No	7 (47%)	3 (13%)
Total	15	24
The Fisher Exact Probability Test reached significance, p=0.03 [1].		

Table 4: Baseline BDNF and treatment response for MDD subjects (N=39) who completed the Study [1].

Results

Initial analysis of our data revealed a wide range of BDNF levels within the MDD group ranging from 10.3 ng/ml to 83.8 ng/ml. The mean serum BDNF level of the entire MDD group was 33.7 ng/ml which was comparable to the value of 34.7 ng/ml in HC subjects. As expected, the difference between the MDD and HC groups did not reach statistical significance (p=0.83).

Therefore in order to further explore the wide spread of values within the MDD group, a median cut off score was computed to be 32.9 ng/ml. Using this cut score, we obtained two subgroups of MDD subjects: a "low" BDNF (N=27) and a "high" BDNF (N=27) subgroup with mean BDNF values of 21.80 ng/ml and 45.57 ng/ml, respectively. Using Levene's test for Equality of Variances and Independent Samples t-test for Equality of Means, the MDD subgroups were compared to the HC group and each other. The mean BDNF value of the HC subjects (34.66 ng/ml) was significantly different than both the "high" (45.57 ng/ml) (p=0.015) and the "low" BDNF group (21.80 ng/ml) (p=0.011). When the two MDD subgroups were compared to each other, they were significantly different (p<0.005) (Table 3).

Mean serum BDNF levels did not differ significantly between male (33.8 ng/ml) and female (33.9 ng/ml) MDD subjects (p=0.991). Mean baseline BDNF levels between MDD subjects older and younger than 40 years old showed no statistically significant difference. One-way ANOVA analysis of mean baseline BDNF levels between Caucasian (N=36, mean=31.3 ng/ml), African-American (N=18, mean=40.4 ng/ml), Hispanic (N=12, mean 31.7 ng/ml) MDD subjects did not show any significant differences (p= 0.112) among ethnicities.

MDD subjects in the "low" BDNF subgroup who had a BMI ≥ 30 (N=16) had significantly higher mean serum BDNF levels in comparison to those who had a BMI ≤30 (N=11) (p=0.032). The "high" BDNF subgroup correlated significantly with subjects who had a BMI ≥ 30 (r=0.248, p=0.043).

Depressed subjects in the "low" BDNF subgroup who had been treated with antidepressant medications up to thirty days prior to the baseline measurement (N=6) had significantly higher BDNF levels of 26.3 ng/ml when compared to subjects with no prior treatment with antidepressant medications (N=10) whose levels were lower at 20.5 ng/ml (p=0.05). Similarly, subjects in the group who had been treated with antidepressant medications more than thirty days of baseline

measurement (N=11) had higher serum BDNF levels of 22.2 ng/ml but these levels were lower than those with antidepressant treatment within thirty days of measurement. However, this difference was not statistically significant (Figure 2).
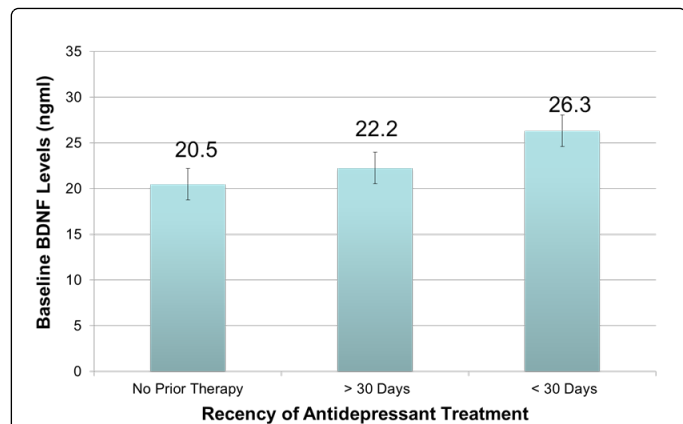
Figure 2: Patients treated with an antidepressant up until 30 days before screening had significantly higher BDNF levels when compared to patients never treated with antidepressants (p=0.05).

In the "high" BDNF subgroup, subjects whose length of depressive episodes was more than six months (N=19), and more than twelve months (N=15), both had statistically significant higher baseline BDNF levels of 47.6 ng/ml and 49.4 ng/ml respectively, in comparison with subjects whose length of depressive episode had lasted between two and six months only (N=6) who were shown to have BDNF levels of 37.3 ng/ml (p=0.03 and p=0.005, respectively). However, there was no significant difference in BDNF levels between subjects with depressive episodes lasting more than six months and those with more than twelve months (Figure 3).
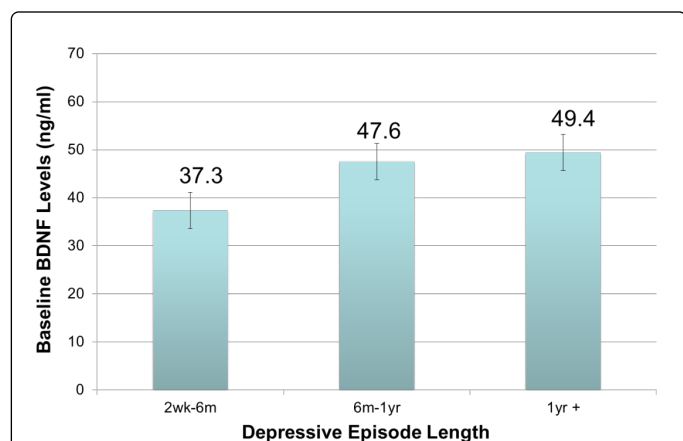
Figure 3: Patients with a depressive episode length greater than 6 months had significantly higher BDNF levels (p=0.03). There was no difference between those whose episode had lasted between 6 months to a year vs. those whose episode had lasted longer than 1 year.

Of the 54 MDD subjects who had baseline BDNF values, 39 completed the study and were assigned a treatment response group. The Fisher Exact Probability Test was used to assess the difference in treatment response between the "low" and the "high" BDNF subgroups. The analysis revealed that 87% of those with high BDNF responded to treatment whereas 53% of patients with low BDNF were responders (p=0.03) (Table 4).

Discussion

The primary goal of this study was to determine whether serum concentrations of BDNF are significantly different in MDD patients as compared to HC subjects and to detect possible subgroups within the entire MDD group. A secondary goal was to explore whether a patient's baseline BDNF level could be related to the patient's length of depressive episode, recent use of antidepressants, and response to antidepressant therapy. The overarching goal of this study was to obtain evidence whether serum BDNF levels can be used as a biomarker of depression and/or predictor of treatment response similar to our previously reported findings with plasma levels of vascular endothelial growth factor [27].

The neurotrophin hypothesis of depression stipulates that loss of BDNF expression in crucial areas of the brain is a key mechanism underlying the pathogenesis of MDD [5,11,12]. Given the evidence supporting this hypothesis and reports that serum levels of BDNF may reflect brain BDNF levels [7,20-24,29,30], we expected serum BDNF levels of MDD subjects would be lower in comparison to HC subjects. Indeed our data showed the average serum BDNF level of the entire MDD group to be somewhat lower than that of HC subjects, although not statistically significant when compared to the HC group. We attribute the lack of statistical significance to the small HC number of analyzed samples in our study that precluded reaching statistical power. However, when we separated the MDD group on the basis of the median value of BDNF into a "low" and a "high" BDNF group, the "low" group was statistically significantly lower than the HC mean. Thus, we believe our findings agree with the findings of Skledar et al. [31] and others who have reported significantly lower levels of BDNF in depressed patients compared to healthy subjects. Our results further parallel those previously reported by several groups of investigators [16,22-24,26,29], who likewise found decreased levels of BDNF in depressed patients compared to HC subjects. To our knowledge, this is the first study to characterize subgroups of MDD subjects based on baseline serum BDNF levels when using the median value to separate a "high" and a "low" subgroup.

It has been suggested that BDNF levels show diurnal variation [32] and this factor requires further investigation as it may aid in the diagnostic differentiation of affectively ill individuals. Despite the growing evidence that serum BDNF levels are reduced in MDD subjects, several factors have limited the adoption of BDNF as a diagnostic biomarker. Foremost amongst them is the fact that BDNF is ubiquitously expressed and secreted in abundance by most peripheral body tissues. In addition to its role in regulating and maintaining neuronal survival of brain circuitry associated with emotion, memory, learning, sleep, and appetite [5,6], emerging evidence also suggests that BDNF may be an important regulator of energy homeostasis. Although serum BDNF levels have been shown to vary with stress, food-intake, and exercise [5,33], we still lack complete understanding of the underlying mechanisms. Very little is known about the source of serum BDNF, its regulation by endocrine or environmental factors, or effects of serum BDNF on the brain. Secondly, reduced serum BDNF levels have been reported in association with a multitude of other psychiatric, neuroinflammatory, and neurodegenerative disorders, including schizophrenia [34], bipolar disorder [35], autism [36],

anorexia and bulimia nervosa [37], Huntington's disease [38], Alzheimer's disease [39], as well as lower respiratory tract infections [14] and type II diabetes [40], thus making serum BDNF a rather nonspecific diagnostic marker.

The association between BDNF levels and age and gender of the patient is also a matter of controversy. No significant difference in serum BDNF levels between male and female subjects, or subjects older and younger than 40 years old was found in our study. Other investigators [41,42] have reported older women have lower BDNF levels compared to younger women and age-matched men. However, lack of sufficient power has been suggested as a reason why some of the previous studies were either unable to detect statistical differences based upon gender [42] or were unable to detect any differences with regard to age of the patient [22,43]. Again searching for subgroups within study groups may reveal statistically significant differences where none are apparent when the entire and ostensibly heterogeneous group is statistically analyzed.

We further obtained evidence that patients with longer duration of depressive episodes tend to have higher levels of serum BDNF suggesting baseline serum BDNF levels do not correlate well with clinical severity of depression. Our findings replicate those of Lang et al who also reported such a negative association [44]. However, a few studies have reported a positive correlation between severity of depression and serum BDNF levels [22,29]. We propose that the higher serum BDNF levels in some of the depressed patients may indicate an attempted neuroprotective effect by specific brain structures in response to the perceived stress associated with the illness of depression. This assumption, however, is predicated on serum levels being directly correlated to brain BDNF concentrations as established in an animal model, but not in humans. Brain-imaging studies have established a decrease in hippocampal volume in patients with depression, likely indicating a process of apoptosis and neuronal loss [8,45-48]. A direct correlation has been established between length of depressive episode and magnitude of hippocampal volume loss [46]. If we assume that serum BDNF levels correlate to cerebral BDNF levels, then an increase in blood BDNF levels in depression may reflect an attempt to shift the balance of the neuronal environment toward neurogenesis thereby protecting against further neuronal damage due to depression and stress.

Our findings indicate that patients who were recently treated with antidepressant medications had the highest levels of serum BDNF as compared to either those who had been treated a long time ago or those whose depression was never treated. We also observed that patients with higher serum BDNF levels had a significantly better response to antidepressant treatment. This response was regardless of prior exposure to antidepressant medication. There is significant evidence that up-regulated BDNF expression is a key target of therapeutic recovery from depression. It is suggested that antidepressant drugs exert their therapeutic action by enhancing BDNF expression in key brain regions resulting in reversal of neuronal atrophy and cell loss [8]. Upregulated expression of BDNF in response to both non-pharmacologic and pharmacologic therapies, e.g., exercise, electroconvulsive therapy, serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, monoamine oxidase inhibitors, and atypical antipsychotic agents, has been shown to oppose stress-induced neuronal damage, restore hippocampal and cortical volume, as well as mediate the behavioral effects of antidepressants [5,19,45,47,49-54].

Study Limitations

Our study results are limited by a relatively low number of MDD and HC subjects for whom BDNF serum levels were available. A further limitation of our study is that we only measured BDNF at a single time point between 9 and 10 am thereby not controlling for circadian rhythm related fluctuations in the levels of serum BDNF as has been indicated in previous studies. This factor could be a confounding variable as a diurnal rhythm may differ between HC and MDD subjects. Such a study would require multiple samplings over a 24-hour period which undoubtedly poses technical difficulties.

Conclusions

We have identified two subgroups of MDD subjects by using the median value as a cut score. Such a differentiation allows more informative comparisons. Low serum BDNF levels may play a role in the pathophysiology of MDD and a higher serum BDNF level prior to the start of therapy with antidepressant medications may be predictive of a positive treatment response. These findings suggest a possible future role for serum BDNF as a useful biomarker of MDD and antidepressant treatment response.

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