

ORIGINAL ARTICLE

LEVELS OF BRAIN DERIVED NEUROTROPHIC FACTOR IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER AND ITS RELATION TO COPING STRATEGIES

Fareeha Butt, Raza ur Rahman*, Ambreen Qamar**, Shazia Nazar**

Department of Physiology, *Psychiatry, Dow Medical College, **Department of Physiology, Ishrat ul Ebad Institute of Oral Health Sciences, Dow University of Health Sciences, Karachi, Pakistan

Background: Brain-derived neurotrophic factor (BDNF) is an effective indicator of Major Depressive Disorder (MDD). The aim of this study was to determine the relation of serum BDNF levels in patients of MDD and association of serum BDNF level with coping strategies. **Methods:** It was a case control study which recruited never treated depressed participants of 18–55 years age. Non-probability (convenience) sampling technique was used. One way ANOVA was applied to investigate the effect of BDNF on COPE, and Spearman's correlation was applied to measure the association between BDNF and Hamilton Rating Scale for Depression (HAM-D). **Results:** There was significant negative moderate correlation between serum BDNF levels and HAM-D (Spearman's $r = -0.29, p = 0.007$) which indicated that more severely depressed patients had lower BDNF scores. There was a significant relationship between BDNF and COPE (Coping Orientation to Problems Experienced) which showed the patients with more Serum BDNF level are coping in a better way ($p = 0.004$). Serum BDNF was significantly lower in patients with emotion focused (Range: 13–17 $\mu\text{g/L}$) and appraised focused (Range: 16.6–20 $\mu\text{g/L}$) group ($15 \pm 4 \mu\text{g/L}$ and $16 \pm 4.8 \mu\text{g/L}$ respectively) than in problem focused (Range: 10–22 $\mu\text{g/L}$) and healthy participants (Range: 18–21.5 $\mu\text{g/L}$) ($18.4 \pm 3 \mu\text{g/L}$ and $20 \pm 5.6 \mu\text{g/L}$ respectively). **Conclusion:** There was a significant relationship between BDNF and COPE, indicating low Serum BDNF level triggered the major depression in which Serum BDNF level was lower in participants of emotion focused and appraised focused group than in problem focused and without MDD group. The inverse moderate correlation was found between serum BDNF levels and HAM-D.

Keywords: Brain Derived Neurotropic Factor, HAM-D, Coping strategies, Major depressive disorder

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INTRODUCTION

Globally, Major Depressive Disorder (MDD) is the most predominant illness among mental, neurological and substance-use disorders,¹ and it is the fourth crucial cause of disability with annual costs of \$80 billion.^{2–4} MDD will be the most susceptible cause of morbidity and mortality in the world by 2020.⁵ In Europe, the prevalence of MDD in adults was fluctuated in between 2% to 6% during last few years.^{6,7}

Brain-derived neurotrophic factor (BDNF) is an effective indicator of MDD.⁸ However, the levels of serum or plasma BDNF are below normal in untreated patients of MDD and the treatment of MDD can restore the decreased to the normal value of BDNF.⁹ Coping is a response to reduce the physical and mental burden which is caused by the tensed life events and routine traumas.¹⁰

METHODS AND MATERIAL

A community based case control study was conducted in Psychiatry OPD in Civil Hospital, Karachi, Dr. Abdul Qadeer Khan Institute of Behavioural Sciences, and Dow Diagnostic Reference and Research Lab (DDRRL) from January 2017 to January 2018. The target population was residents of Karachi. Participants of any gender aged 18–55 years, never treated for depression,

and who provided written informed consent, were included in the study. Patients with mental retardation, substance abuse, organic disorders such as dementia, epilepsy, cerebrovascular accident, psychosis, bipolar disorders, who had history of steroid treatment, and those with acute/chronic physical illness, were excluded. Sample size was calculated as 84 with Open-Epi sample size calculator. Forty-two (42) cases (antidepressant-free outpatients with MDD) and forty-two (42) controls (age matched healthy volunteers) were selected. Non-probability (convenience) sampling technique was used.

Quantitative determination of human BDNF concentrations was done with a Human BDNF ELISA Kit by Glory Science Co., Ltd Catalogue #10186. The patients were rated by a clinician on HAM-D 17 items scored either on a 3-point or 5-point Likert-type scale. Scores ranging from 0 to 54. HAM-D scores were classified as normal (<9), mild depression (10–13), mild to moderate depression (14–17), and moderate to severe depression (>17).

Coping strategies were determined with the help of brief cope scale. It is a 28-item scale. The overall coping strategy is determined by looking individually at each patients scale with the help of clinical psychologist. The patients were divided into three groups according to

their answers as problem focused, appraisal focused, and emotion focused.

The data was kept anonymous and confidential and the written informed consent was taken before collecting data. The study protocol was approved by the Institutional Review Board of the University (Reference number IRB 572/DUHS/Approval 2015/87).

At univariable stage with categorical variables Chi-square test was executed to measure the association of cases and controls with different demographic characteristics, with quantitative variable, Mann Whitney-Wilcoxon test was used to compare the Mean±SD of cases and controls with age and income. Chi-square test was also executed to measure the association of coping categories with different demographic characteristics.

One-way ANOVA was applied to investigate the effect of BDNF on COPE (Coping Orientation to Problems Experienced) and demographic variables. Kruskal-Wallis test was applied to investigate the effects of HAM-D on demographic variables. Spearman's correlation was applied to measure the strength of association between BDNF and HAM-D.

RESULTS

A total of 84 subjects with 1:1 ratio of case and control were included in the study. The average BDNF of participants was 18±5 µg/L with range of 6.8 to 29.7 µg/L. The average HDRS of participants was 13±10 with 3 to 34 ranges. Half of the participants were depressed and remaining were not depressed, in which most of patients were belonging to emotion focused coping strategy (n=23), 14 (17%) were using problem focused, and 5 (6%) were using appraised focused strategy.

The significant association of cases and controls was calculated with education in which controls were mostly illiterate (n=12) than cases (8, 19%, p=0.004). Occupation was also associated with cases and controls; the prevalence of cases was high in unemployed (57%) (p=0.01). Income status was significantly associated with cases and controls (p=0.05), the participants who were earning less than Rs. 10,700 and Rs. 10,701 to 20,000 Rs per month, were almost equally susceptible to be in cases (57% and 24% respectively). There was no significant association of cases and controls with age, gender, marital status, income and family type (Table-1).

There was significant negative moderate correlation between serum BDNF levels and HAM-D (Spearman's r= -0.29, p=0.007) indicating that more severely depressed patients had lower BDNF scores.

There was a significant relationship between BDNF and COPE which showed the patients who had higher Serum BDNF level are better at coping. (p=0.004). Serum BDNF was significantly lower in

patients with emotion focused (Range: 13–17 µg/L) and appraised focused (Range: 16.6–20 µg/L) group (15±4 µg/L and 16±4.8 µg/L respectively) than in problem focused (Range: 10–22 µg/L) and healthy participants (Range: 18–21.5 µg/L) (18.4±3 µg/L and 20±5.6 µg/L respectively) (Table-2).

Table-1: Demographic characteristics of Cases and Controls [n (%)]

Variables	Case	Control	p
Age (Mean)†	40	45	0.99†
<20 Years	6 (14.3)	7 (16.7)	0.22‡
21–30 Years	19 (45.2)	10 (23.8)	
31–40 Years	12 (28.6)	18 (42.9)	
41–50+ Years	5 (11.9)	7 (16.7)	
Gender			
Male	16 (38)	19 (45)	0.51‡
Female	26 (62)	23 (55)	
Marital Status			
Unmarried	20 (48)	16 (38)	0.37‡
Married	22 (52)	26 (62)	
Education			
Illiterate	8 (19)	12 (29)	0.004‡
Matric	20 (48)	5 (12)	
Intermediate	3 (7)	8 (19)	
Graduate (<16 Years)	11 (26)	17 (40)	
Postgraduate (>16 Years)	0 (0)	0 (0)	
Occupation			
Unemployed	24 (57)	15 (36)	0.01‡
labour work	9 (22)	22 (52)	
Professional	9 (21)	5 (12)	
Income (Mean)†	41	44	0.67†
<10,700	24 (57)	23 (55)	0.05‡
10,701–20,000	10 (24)	12 (28)	
20,001–25,000	3 (7)	0 (0)	
25,001–35,000	5 (12)	2 (5)	
35,001–50,000+	0 (0)	5 (12)	
Family Type			
Nuclear	28 (67)	26 (62)	0.64‡
Joint	14 (33)	16 (38)	

†Mean, Mann-Whitney test applied, ‡Chi-square test applied

Table-2: The Relationship of BDNF with COPE

Variables	n	Mean ±SD	95% CI		p
			Lower	Upper	
COPE					
Emotion focused	23	15±4	13	17	0.004*
Problem focused	14	18.4±3	16.6	20	
Appraised focused	5	16±4.8	10	22	
Without MDD	42	20±5.6	18	21.5	

One way ANOVA applied, MDD=major depressive disorder.

Demographic characteristics such as age, gender, marital status, educational status, family type, income and occupation of the participants were not significantly associated with serum BDNF. Occupation (p=0.02), education status (p=0.01) and income (p=0.04) were significantly related to HAM-D (Table-3).

The coping strategies were not significantly associated with age (p=0.12), gender (p=0.09) and income per month (p=0.12) of the participants, in contrary, different coping strategies were show significant association with marital status (p=0.05), educational status (p=0.009), occupation (p=0.006) and family type (p=0.03).

In marital status, most of the unmarried participants with MDD were found in appraised focused (80%) and emotion focused (57%) coping group and just 24.1% were found in problem focused group. On the other side, 78.60% of married participants with MDD were found in problem focused group, 43% were in emotion focused and remaining few were in appraised focused.

In educational status, high frequency of illiterate participants with MDD were originate in problem focused (28.6%), 17.4% were in emotion focused and unfortunately no one originate in appraised focused. Bulk of the participants with MDD who were done matric was in appraised focused (60%) group, half of them were in emotion focused (52%) and remaining 35.7% were in problem focused. Majority of participants with MDD who have done intermediate in appraised focused group, few of them were in emotion focused (4.3%) and no one found in problem focused. Most of the graduate participants with MDD were in problem focused (35.7%) continuing were in emotion focused group (26.1%) and 0% were evaluated in appraised focused. Over all frequency of post graduate participants with and without MDD were nil.

Table-3: The Relationship of Demographic characteristics with BDNF and HDRS/HAM-D

Variable	BDNF			HDRS		
	n	Mean±SD	p	n	Mean	p
Age						
<20 years	13	17.3±4.6	0.3†	13	42.77	0.2‡
21–30 years	29	17.2±5.0		29	49.64	
31–40 years	30	18.2±5.4		30	38.68	
41–50+ years	12	20.4±5.2		12	34.5	
Gender						
Male	35	18.7±4.7	0.36†	35	37.6	0.17‡
Female	49	17.6±5.4		49	46	
Marital status						
Unmarried	36	17.2±4.9	0.18†	36	44.47	0.51‡
Married	48	18.7±5.3		48	41.02	
Occupation						
Unemployed	39	17.4±5.1	0.52†	39	48.83	0.02‡
Labour work	31	18.4±5.8		31	32.97	
Professional	14	19.1±3.4		14	45.96	
Education Status						
Illiterate	20	18.5±6.0	0.5†	20	37.62	0.01‡
Matric	25	16.9±4.2		25	55.3	
Intermediate	11	19.6±5.6		11	35.23	
Graduate (<16 Years)	28	18.1±5.1		28	37.41	
Postgraduate (>16 Years)	0	0		0	0	
Family type						
Nuclear	54	18.2±5.2	0.71†	54	40.99	0.44‡
Joint	30	17.8±5.1		30	45.22	
Income						
<10,700	47	18.1±5.2	0.67†	47	44.09	0.04‡
10,701–20,000	22	17.8±5.9		22	35.45	
20,001–25,000	3	14.4±3.4		3	68.67	
25,001–35,000	7	18.6±2.2		7	54.86	
35,001–50,000+	5	20±5.2		5	25.6	

†One-way ANOVA applied, ‡Kruskal-Wallis test applied

In occupation, majority of unemployed with MDD were calculated in emotion focused group, 40% in appraised and remaining 35.7% were in problem focused. More than half of MDD participants who were doing labor work, were calculated in appraised focused group. 35% of professional participants with MDD were in problem focused.

In family type, most of the participants with MDD who were belonging to nuclear family type were evaluated in appraised focused, 85.7% were in problem focused and 47.8% in emotion focused. More than half of the MDD participants who were belonging to joint family type were in emotion focused.

DISCUSSION

Considering the first case control study to assess the relationship between serum BDNF and MDD in drug naïve patients. A notable finding of our study was a significant relationship between serum BDNF level and Coping strategies, indicating low Serum BDNF level trigger the major depression. Serum BDNF level was lower in participants of emotion focused and appraised focused group. Moreover, the negative moderate correlation was established between the level of BDNF and HAM-D.

Our study revealed the non-significant association among the age and gender of the patients of major depressive disorder and control (healthy participants). In contrary, Molendijk ML, *et al*¹¹ found a significant association among age and female gender of the patients of major depressive disorder who were not taking any anti-depressant. The plausible reason to have MDD in female compared to male is that women face individual and social factors that would be main reason to have depression including difference in expressions of psychological distress, harassment and multiple responsibilities.¹²

There was a non-significant association of marital status with MDD in our study. This finding was not consistent with the study done in University of Southern California¹² reporting that never married, separated, or divorced had lower risk of 12 month MDD than married participants. However, the finding of University of California was not consistent with previous few studies¹³ indicating married adults have lower rates of depression as compare to unmarried participants and married older adults have a lower occurrence of lifetime mood disorders. This difference in results was due to different methodologies and patients from different sociocultural setup, and also due to use of different scales. Although, early marriages and subsequent divorces were main causes to have psychiatric disorders.¹²

Even though, our study exposed that education had significant association with cases and controls; high HAM-D was found in participants who had done

secondary education than those who were illiterate and well educated. Our finding was concurrent with previous study conducted in Netherlands¹¹ that participants of control groups had high mean of education in years than participants of MDD with significant association. Plausible reason of high prevalence of MDD in participants of secondary education was the uncertainty in job status¹⁴ and low prevalence of MDD in educated group is that they have good awareness regarding depressive disorders in order to cope with it and increasing levels of education is a defensive factor against MDD.¹⁵

In our study, Income was significantly associated with cases and controls, the participants who were earning smaller than Rs. 20,000 per month, were susceptible to have MDD. Participants who were earning Rs. 20,001 to 25,000 per month had highest HDRS then those who were earning >25,000 rupees per month. Similarly, a study of USA⁸ proportionally shared that the poverty income ratio and smoking status were significantly associated with MDD symptoms in black women. Even though, after controlling the all other socioeconomic and fitness variables, black women below 299% federal poverty level were three times more susceptible to have symptoms of MDD than black women above 300% federal poverty level. Plausible reason to have high risk of MDD in low socioeconomic group was the non-employment and low income.¹⁴

Our study explored the significant relationship between types of occupation and MDD in which the prevalence of cases was high in unemployed and professional groups of participants. HAM-D was high in unemployed and professional participants as compare to participants who were doing labour work. This finding was almost similar to a previous study on Chinese women in 2014¹⁵, large effects of MDD were seen for occupation and education. Unemployment increases the risk of MDD than in employed. In this study, retired were five folds more susceptible to have MDD than three folds to unemployed. Main reasons to have low prevalence of MDD in professional group is that fewer participants were found in this group and we could not found good frequency of participants in cases.

The socio-economic status (SES) is defined in a comparatively simplistic form, which containing differences in employment status, social class (by occupation), and education. The occupation and education were predictable to be the key modules of social status and these two modules were used to measure the relation between socio-economic status and MDD.¹⁶⁻¹⁸ However we did not include data on living style or material possessions, these variables would be the key modules to explore the relationship between wealth and MDD. Our findings are vigorous, we reported the true factors that would be in the association of the variable that we obtained.

This study also illustrated that significant negative moderate correlation between serum BDNF level and HAM-D was indicating that more severely depressed patients had lower BDNF scores. Our finding is complemented by previous study conducted by Varambally S *et al*¹⁹. This previous research highlighted that serum BDNF level was significantly lower in patients with cases in comparison with controls, and a significant negative correlation was also found between serum BDNF levels and HAM-D. Moreover, the negative correlation between severity of depression and BDNF levels was evaluated with previous study of Japan.²⁰ Reason behind the relationship between BDNF and MDD, BDNF is present in both the central and peripheral nervous system and it is also a modulator of neuroplasticity in the brain which deals with neuronal survival, synaptic signalling and synaptic consolidation.

As per our study, there was a significant relationship between BDNF and COPE which showed the patients had more serum BDNF levels, the more they got normal. Serum BDNF was significantly lower in patients with emotion focused and appraised focused group than in problem focused and healthy participants. However, the relationship between depression and coping strategies was found before but the review of literature shows that this is the unique study that shows the possible relationship between the levels of BDNF and coping strategies.²¹⁻²³ Nevertheless, It was assumed that the depressed patients with the lowest serum BDNF levels will use emotion focused coping and the patients with relatively higher serum BDNF levels will use appraisal focused coping and those among depressed who have the highest serum BDNF level will use problem solving coping.

In inferential statistic of our study, the coping strategies (emotional, problem and appraisal focused) were not significantly associated with age, gender and income of the participants. In contrary, different coping strategies were significantly associated with marital status, educational status, occupation and family type. Unfortunately, there was no previous data related to the coping strategies of our study and demographic variables (age, gender, income, marital status, educational status, occupation and family type).

CONCLUSION

Participants who had low level of education, unemployed status and less income per month were more susceptible to have MDD. There was a significant relationship between BDNF and COPE indicating low serum BDNF level, trigger the major depression. The serum BDNF level was lower in participants of emotion focused and appraised focused group than in problem focused and without MDD group. The inverse moderate correlation was found between serum BDNF levels and HDRS. Occupation, education, and income had

dominant association with HAM-D in which almost similar susceptibility of MDD were found in unemployed and professional participants. Matric passed participants were having high HAM-D score. Participants who were earning average income were more susceptible to have high HAM-D score.

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Address for Correspondence:

Dr Fareeha Butt, Assistant Professor, Department of Physiology, Dow Medical College, Dow University of Health Sciences, Karachi, Pakistan. **Cell:** +92-331-2602355

Email: fareeha.butt@duhs.edu.pk

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FB: Concept, Analysis, Interpretation

RR: Concept, Revising

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