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ORIGINAL ARTICLE

Association of Serum Level and DNA Methylation Status of Brain-Derived Neurotrophic Factor with the Severity of Coronary Artery Disease

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ABSTRACT

Background and Aim: Brain-derived neurotrophic factor (BDNF) has shown to promote myelination besides its effect on survival, differentiation, and plasticity of neurons. It has an important role in maintaining cardiovascular health in addition to its central nervous system function. The present study aimed to determine the serum level association with DNA Methylation status of brain derived neurotrophic factor with severity of coronary artery disease.

Methods: This cross-sectional study was carried out on 164 major coronary artery patients in the department of Biochemistry & Pharmacology of Bahawal Victoria Hospital Bahawalpur from April 2022 to December 2022. Individual with possible cardiac symptoms such as chest pain and dyspnea were enrolled. Patients were distributed as CAD group (n=82) and non-CAD group (n=82). CAD severity was measured by Gensini scoring system. The coronary artery lumen stenosis was defined as follows: 1, 2, 4, 8, 16, and 32 was for 1-25%, 26-50%, 51-75%, 76-90%, 91-99%, and total occlusion respectively. Prior to angiography, patients' anthropometric parameters such as BMI, systolic, and diastolic pressure were recorded. Demographic details such as age, gender, and smoking status were also noted. SPSS version 27 was used for data analysis.

Results: Of the total 164 patients, there were 82 study group comprised of 58 (70.7%) male and 24 (29.3%) females whereas control group was comprised of 40 (48.8%) male and 42 (51.2%) females. Study group had at least one major coronary artery with > 50% stenosis classified as CAD group and non-CAD group patients had completely normal coronary angiographies. The CAD group patients had higher mean age and smokers than non-CAD group. The incidence of hypermethylated BDNF gene in CAD and non-CAD group was 86.6% and 70.7% respectively. There were insignificance difference of serum BDNF concentration mean values in CAD group (1.82 [1.61-2.12] ng/ml) versus non-CAD group (1.69 [1.39-2.03]). The BDNF methylation was found 81.2% in male and 83.4% in female patients. Regarding serum BDNF mean value, no significance difference was observed in men (1.82 [1.52–2.12]) and women (1.70 [1.44–2.02]).

Conclusion: The present study concluded that the increased risk of CAD associated with BDNF hypermethylation may be useful for identifying subjects at risk. A significant correlation was also found between BDNF hypermethylation and CAD severity. There was no significant association between severity of CAD and BDNF serum level.

Keywords: Brain-derived neurotrophic factor, serum level, Coronary artery disease, Severity, DNA methylation

INTRODUCTION

The brain-derived neurotrophic factor (BDNF) supports the development, survival, and maintenance of neurons [1]. Modern research has shown that receptors of BDNF are present in the peripheral vasculature, where it promotes endothelial cell survival, angiogenesis, and vascular integrity [2-4]. Blood contains BDNF as well [5]. Plasma BDNF levels have been found to be lower in individuals with cardiovascular disease [6-8]. Additionally, reduced blood BDNF levels have been associated to an increased risk of severe cardiovascular events and death in individuals with coronary artery disease (CAD) [9]. High BDNF levels, on the other hand, were related with a lower risk of cardiovascular disease and death in a large community-based cohort [10].

A variety of factors impact BDNF levels circulation. Reduced BDNF levels have been linked to recognized CAD risk factors such as old age, smoking, diabetes mellitus, lipid levels, and physical dormancy [11-13]. Subsequent clinical investigations have found a connection between endothelial dysfunction and BDNF levels circulation [14] and hypertension [15]. As a result, we postulated that a significant contributor to decreased circulating levels of BDNF in CAD patient's endothelial dysfunction.

Coronary artery disease (CAD) is a significant cause of mortality globally [16]. Dyslipidemia, hypertension, smoking, obesity, and diabetes have all been identified as CAD-related key clinical risk factors. BDNF lower serum has been related to a higher incidence of CAD related risk factors and mortality [17]. In contrast, Wang et al., reported that BDNF higher amount was present in vascularized coronary may be deleterious to plaque stabilization [18]. Aberrant DNA methylation has been linked to the genesis and progression of CAD and atherosclerosis [19].

No studies on the BDNF gene methylation status in CAD in humans have been published. As a result, the current study aimed to investigate the gene methylation status association with blood level of BDNF in CAD patients, as well as their relationship to CAD risk and severity.

METHODOLOGY

This cross-sectional study was carried out on 164 major coronary artery patients in the department of Biochemistry & Pharmacology of Bahawal Victoria Hospital Bahawalpur from April 2022 to December 2022. Individual with possible cardiac symptoms such as chest pain and dyspnea were enrolled. Patients were distributed as CAD group (n=82) and non-CAD group (n=82). CAD severity was measured by Gensini scoring system. The coronary artery lumen stenosis was defined as follows: 1, 2, 4, 8, 16, and 32 was for 1-25%, 26-50%, 51-75%, 76-90%, 91-99%, and total occlusion respectively. Prior to angiography, patients' anthropometric parameters such as BMI, systolic, and diastolic pressure were recorded. Demographic details such as age, gender, and smoking status were also noted. Individual age < 18 years old, having any thyroid disorders, mental diseases, malignancy, any history of cardiovascular disease, antidepressant or tranquillizers, and chronic inflammatory diseases are all excluded. Blood samples of fasting peripheral venous were collected and clotted at room temperature for spam of 1 hour. Standard laboratory procedures were used to quantify high-density lipoprotein cholesterol (HDL-C), serum triglyceride (TG), total cholesterol (TC), and fasting blood glucose (FBS).

SPSS version 27 was used for data analysis. Categorical variables were reported as frequencies and percentages, and the Chi-square test was employed to analyze them, to determine the relationship between clinical variables and BDNF methylation. All the descriptive statistics was done by taking 95% confidence intervals (CI), and 5% level of significance.

RESULTS

Of the total 164 patients, there were 82 study group comprised of 58 (70.7%) male and 24 (29.3%) females whereas control group was comprised of 40 (48.8%) male and 42 (51.2%) females. Study group had at least one major coronary artery with > 50% stenosis classified as CAD group and non-CAD group patients had completely normal coronary angiographies. The CAD group patients had higher mean age and smokers than non-CAD group. The incidence of hypermethylated BDNF gene in CAD and non-CAD group was 86.6% and 70.7% respectively. There were insignificance difference of serum BDNF concentration mean values in CAD group (1.82 [1.61-2.12] ng/ml) versus non-CAD group (1.69 [1.39-2.03]). The BDNF methylation was found 81.2% in male and 83.4% in female patients. Regarding serum BDNF mean value, no significance difference was observed in men (1.82 [1.52–2.12]) and women (1.70 [1.44–2.02]). Table-I represent the demographic details of CAD and non-CAD group patients. Clinical and biochemical parameters of both groups are shown in Table-II. Individuals' demographic, clinical, and biochemical parameters were determined using the Gensini score are shown in Table-III. Correlation of the clinical and biochemical characteristics with BDNF gene methylation status is shown in Table-IV.

Table-1: demographic details of CAD and non-CAD group patients

Parameters	CAD group (N=82)	Non-CAD group (N=82)	P-value
Age (years)	52.69 ± 1.14	49.68 ± 1.23	<0.001
Gender N (%) Male Female	 58 (70.7) 24 (29.3)	 40 (48.8) 42 (51.2)	
BMI (kg/m^2)	24.36 ± 0.48	25.17 ± 0.62	0.001

Table-2: Clinical and biochemical parameters of both groups

Parameters	CAD group (N=82)	Non-CAD group (N=82)	P-value
SBP	134.42 ± 2.46	130.12 ± 3.19	<0.001
DBP	80.87 ± 1.21	78.64 ± 1.52	0.218
Serum BDNF (ng/ml)	2.19 ± 0.17	2.01 ± 0.13	0.082
FBS (mg/dl)	92.62 ± 1.42	90.52 ± 1.52	0.692
TG (mg/dl)	138 [99–179.6]	119 [91–180]	0.367
Total cholesterol (mg/dl)	160.98 ± 3.85	166.23 ± 5.17	0.009
HDL-C (mg/dl)	41.69 ± 1.51	44.51 ± 1.61	0.008
LDL-C (mg/dl)	88.32 ± 4.42	92.82 ± 4.25	0.153
Platelet (9 10^3/µl)	228.12 ± 7.79	227.11 ± 9.57	0.528

Table-3: Individuals' clinical, and biochemical parameters were determined using the Gensini score

Parameters	Mild CAD group (N=36)	Severe CAD group (N=46)	P-value
SBP	133.31 ± 3.42	136.4 ± 3.25	0.583
DBP	81.25 ± 1.89	81.84 ± 1.52	0.431
Serum BDNF (ng/ml)	2.24 ± 0.21	2.25 ± 0.232	0.423
FBS (mg/dl)	93.12 ± 2.36	90.62 ± 1.64	0.628
TG (mg/dl)	136.5[105–192]	139 [90–182]	0.367
Total cholesterol (mg/dl)	161.25 ± 5.65	163.52 ± 6.69	0.752
HDL-C (mg/dl)	40.59 ± 2.31	41.82 ± 1.92	0.428
LDL-C (mg/dl)	88.03 ± 5.68	90.21 ± 5.89	0.834
Platelet (9 10^3/µl)	221.23 ± 12.25	231.63 ± 9.72	0.329

Table-4: Correlation of the clinical and biochemical characteristics with BDNF gene methylation status

Parameters	Methylated N=71 (86.6%)	Un-methylated N=58 (70.7%)	OR 95% CI	P-value
SBP	134.41 ± 1.98	128.32 ± 3.59	1.02 (0.987–1.029)	0.367
DBP	81.32 ± 0.97	80.4 ± 1.95	1.021 (0.985–1.067)	0.431
Serum BDNF (ng/ml)	2.10 ± 0.19	2.31 ± 0.225	1.82 [1.61-2.12]	0.392
Smoking (Y/N)	39/32	37/21	4.842 (0.425–62.229)	0.239
Aspirin medication (Y/N)	60/11	45/13	1.492 (0.542–4.236)	0.393
Statin medication (Y/N)	47/24	39/19	0.997 (0.415–2.457)	0.899
TG (mg/dl)	139 [95–180]	138 [92–180]	1.012 (1.001–1.019)	0.021
Total cholesterol (mg/dl)	165.82 ± 3.18	150.31 ± 7.24	1.009 (0.879–1.019)	0.078
HDL-C (mg/dl)	41.78 ± 1.19	42.89 ± 2.49	0.897 (0.859–1.034)	0.756
LDL-C (mg/dl)	91.89 ± 3.75	82.12 ± 6.89	1.005 (0.898–1.021)	0.326

DISCUSSION

The present study mainly investigated the serum level association with DNA methylation status of brain and found that a higher risk of CAD related with BDNF hyper methylation may be beneficial for identifying patients at risk. A strong relationship was also discovered between the CAD severity and BDNF hyper methylation. The blood BDNF level was not related to CAD severity. Due to BDNF part in encouraging neuron development, survival, and regeneration, BDNF has received a lot of attention in recent years. Yet, there have been few findings on the BDNF role outside the nervous system. Recent data suggests that BDNF plays an important role in cardiovascular function [20]. There was a significant reduction in BDNF levels in patients with stable CAD when compared to control patients. According to a small case-control study comparing ACS patients with controls, plasma BDNF levels were lower in ACS patients. Peripheral and central neurological system generates the circulating BDNF [21] and non-neural organs such as muscles, endothelial cells, and immunocytes [22, 23]. BDNF travels from the brain to the bloodstream via the blood-brain barrier [24].

The current study found that BDNF gene methylation was significantly lower in non-CAD group as compared to CAD group. Other research examined the connection between BDNF methylation and individual's depression with acute coronary syndrome [25]. Liu et al., [26] investigated the relationship between hyper methylation of BDNF gene and acute coronary syndrome depressive disorder in patients. Their findings showed that BDNF hyper methylation was related to vulnerability to initial depressing disease and improved treatment response of antidepressant in ACS [27].

We found no correlation between status of gene methylation and circulating BDNF levels in the current study. Thus far, no investigation has examined the connection between blood levels and BDNF methylation in individuals with CAD. A prior study on healthy women (aged 20 to 80 years) found that BDNF gene DNA hyper methylation was not substantially related to blood BDNF levels. They determined that BDNF gene hyper methylation could not directly cause a drop in blood BDNF levels [28].

Nakamura et al., [29] evaluated the coronary circulation BDNF level among 45 stable and 38 unstable angina in comparison to healthy group (n=24) [30]. There was no statistically variation in BDNF levels has been found among these groups. Yet, as compared to persons with stable angina or the control group, and unstable angina patients had a considerable rise in BDNF levels in the coronary circulation. This showed that BDNF may be implicated in plaque instability [31]. In contrast, Jiang et al. discovered reduced plasma BDNF concentrations in patients with angina pectoris compared to healthy controls [32].

As previously reported BDNF levels and plasma declined with advancing age [33]. Similarly, another study [34] reported that low BDNF levels were related with diabetes mellitus and elevated LDL levels. Patients with low BDNF levels had higher vWF levels,

which might indicate endothelial dysfunction. Second, physical training has been shown to boost peripheral BDNF levels in people [35] and to increase BDNF expression in animal endothelial cells. Finally, hypertension [36] and type 2 diabetes [37] are linked to lower endothelial BDNF expression.

CONCLUSION

The present study concluded that the increased risk of CAD associated with BDNF hypermethylation may be useful for identifying subjects at risk. A significant correlation was also found between BDNF hypermethylation and CAD severity. The serum BDNF level was not associated with CAD risk or severity.

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