Prognostic significance of brain-derived neurotrophic factor levels in patients with heart failure and reduced left ventricular ejection fraction

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Abstract

Objective: Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family. The aim of the present study was to investigate the relationship between BDNF levels and prognostic markers in patients with heart failure (HF) and reduced left ventricular ejection fraction (LVEF), considering death or rehospitalization due to HF.

Methods: Patients with severe left ventricular systolic dysfunction (LVEF ≤35%) and individuals with no history of cardiac disease (control group) were included in the study conducted between 2013 and 2017. Of the included patients, 52 were classified as mildly symptomatic [New York Heart Association (NYHA) I–II], and 108 were classified as severely symptomatic (NYHA III). The control group comprised 50 individuals. The primary endpoints of the study consisted of cardiovascular death during long-term follow-up and hospitalization for worsening of HF.

Results: The mean age of the patient group was 67.60±11.45 years and 58% were male, whereas that of the control group was 66.28±11.30 years and 48% were male. The N-terminal pro-brain-type natriuretic peptide (NT-pro-BNP) serum levels in patients with HF were higher, whereas the BDNF values were lower than those in the control group (NT-pro-BNP: 5010±851 pg/mL vs. 33±11 pg/mL, p<0.001; BDNF: 8.64±1.12 ng/mL vs. 17.58±4.51 ng/mL, p<0.001). Multivariable analysis suggested that there was a significant association between BDNF levels and clinical status, generating the primary endpoints of death [BDNF levels: Odds ratio (OR)=0.17, 95% confidence interval (CI): 0.05–0.53, p=0.002], and rehospitalization (BDNF levels: OR=0.702, 95% CI: 0.54–0.92, p=0.010).

Conclusion: Decreased serum BDNF levels were associated with death and rehospitalization in patients with HF, suggesting that these levels can be useful prognostic biomarkers. *(Anatol J Cardiol 2019; 22: 309-16)*

Keywords: brain-derived neurotropic factor, N-terminal pro-brain-type natriuretic peptide, heart failure, New York Heart Association

Introduction

Heart failure (HF) is a complex and progressive clinical syndrome, which is a result of structural and functional disorders, eventually leading to a failure to pump the required amount of blood for peripheral tissue metabolism (1). HF is highly prevalent worldwide. Owing to frequent hospitalizations and high morbidity and mortality rates, it has a high economic burden on health expenditure (2). Although there are several biomarkers for the diagnosis and prediction of prognosis in patients with HF, natriuretic peptides are the most commonly evaluated; they have been reported to be useful for diagnosis, prediction of prognosis, and risk assessment (3). However, there are some limitations in the employment of natriuretic peptides as biomarkers in patients with HF, such as obesity, kidney failure, age, and low specificity (4, 5). Therefore, novel biomarkers are required for clinical judgment.

Neurotrophins are members of the polypeptide-structured growth factor family and are intracellular factors that affect the survival and functions of neurons and control synaptic function and plasticity (6). They are synthesized from neurons in the central and peripheral nervous systems and from several cell types

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in peripheral tissues. Furthermore, it is known that they have a biological effect on many tissues both in and out of the nervous system (7). The brain-derived neurotrophic factor (BDNF), which was defined as the second member of the growth factor family after nerve growth factor, was first isolated from the pig brain tissue (8). In addition to brain tissue, BDNF mRNA expression has been detected in the heart, great vessels, lung tissue, spleen, smooth muscle cells, kidney, bladder, and visceral epithelial cells (7).

Recently, many studies in rats and humans have shown the association of BDNF with cardiovascular diseases (9, 10). Reduced BDNF is associated with cognitive dysfunction in patients with chronic HF (11). Moreover, the prognostic significance of BDNF has been demonstrated in patients with hypertension, diabetes, Chagas' cardiomyopathy, HF, and coronary artery disease (CAD) (12-17). There is no comprehensive study investigating the prognostic significance of BDNF in patients with HF with severe left ventricular systolic dysfunction. Thus, the aim of the present study was to investigate the relationship between BDNF and NT-pro-BNP levels and prognostic markers, consisting of death and rehospitalization due to HF as the primary endpoints, in patients with HF with severe left ventricular systolic dysfunction.

Methods

The present study was conducted between February 2013 and March 2017. Patients with severe left ventricular systolic dysfunction [left ventricular ejection fraction (LVEF) ≤35%] were included in the study. Fifty-two patients were classified as mildly symptomatic [New York Heart Association (NYHA) I–II], and 108 were classified as severely symptomatic (NYHA III). Furthermore, 50 age- and sex-matched individuals with no history of cardiac disease were included as the control group (Fig. 1). Demographic and clinical characteristics and 12-lead electrocardiograms of the participants were recorded. The study was approved by the Institutional Ethical Committee according to the Declaration of Helsinki. Written informed consent was obtained from all participants of the study. All patients were followed up at a specialized specific HF outpatient clinic and staffed with an expert team comprising one academic resident, one cardiology resident, and one nurse. Timely relevant clinical practice guidelines that recommended evidence-based therapies and management strategies were administered to each patient in a personalized manner at periodic intervals. The primary endpoints of the study comprised cardiovascular death during long-term follow-up and hospitalization for worsening of HF. Cardiac death was defined as death due to worsening of HF or sudden cardiac death, and HF hospitalization was defined as an unplanned hospital admission requiring intravenous diuretics, vasodilators, or inotropic agent infusion. Moreover, cardiac death during rehospitalization was counted as a single event.

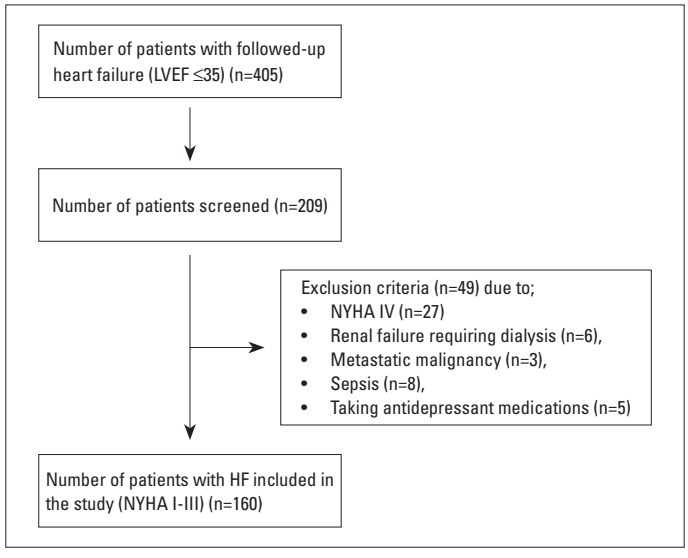

Figure 1. Flowchart of patients in the study

Based on the standard criteria and the presence of systolic or diastolic functional impairment, HF was diagnosed by two cardiologists using echocardiography according to the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines (18). Transthoracic echocardiography examination was implemented using an X5-1 transthoracic probe echocardiography device. According to the recommendations of the American Society of Echocardiography, the standard evaluation included M-mode, 2-dimensional, and Doppler studies (19). LVEF was calculated by the Simpson method from apical four-chamber images, and diastolic and end-systolic endocardial margins were manually traced in all the sections from the apex to the base (20). The term "advanced HF" is used to characterize patients with severe symptoms, recurrent decompensation, and severe cardiac dysfunction. Severe left ventricular systolic dysfunction has been accepted as LVEF ≤35% (21).

The NYHA functional classification has been used to describe the severity of symptoms and exercise intolerance. Two cardiologists classified the HF of the patients according to the severity of their symptoms. They placed patients in one of the four categories based on how limited they were during physical activity: NYHA I–no limitation of physical activity, NYHA II–slight limitation of physical activity, comfortable at rest, and ordinary physical activity resulting in fatigue, palpitation, or dyspnea (shortness of breath), NYHA III–marked limitation of physical activity, comfortable at rest, and less than ordinary activity causing fatigue, palpitation, or dyspnea, and NYHA IV–unable to perform any physical activity without discomfort (22). Patients were excluded from the study if they presented with any of the following within 2 weeks before the study: changes in NYHA functional class, changes in HF medications, or the administration of any intravenous medication for HF.

Patients with severe non-cardiac comorbidities, such as vital organ disease with severe organ dysfunction, renal failure

requiring dialysis, metastatic malignancy, and sepsis/septic shock, as well as pregnant patients and subjects <18 years old were also excluded from the study. In addition, patients were excluded if they had signs of or a history of a psychiatric disorder, such as major depressive disorder, schizophrenic disorder, and organic brain disorders, or those under antidepressant medications, experienced a stroke within the past 3 months, or unable to perform a maximal exercise test because of a neurologic deficit.

BDNF and NT-pro-BNP analysis method

Peripheral venous blood samples were collected in serum tubes from all the subjects between 6:00 am and 9:00 am. All samples were allowed to clot before being centrifuged at 1000 g for 15 min and were stored at −80°C until analysis. Serum BDNF levels were determined by a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Bioassay Technology Laboratory, Shanghai, China) according to the manufacturer's protocol; its detection limit was set at 20 pg/mL. To ensure accurate measurements, all the samples were analyzed in duplicate by investigators blinded to the clinical information. Additionally, plasma NT-pro-BNP was measured by means of an ELISA kit (Bioassay Technology Laboratory).

Statistical analysis

SPSS (Statistical Package for Social Sciences for Windows; IBM Corp., USA) 19.0 program was used for statistical analysis. Findings were expressed as mean±standard deviation and percentage (%) for descriptive statistics. Kolmogorov–Smirnov and Shapiro–Wilk tests were used to evaluate the normal distribution of the variables, as appropriate. Student's t-test or Mann–Whitney U test was used to evaluate the relationships between continuous and categorical variables, as indicated. Chi-square or Fisher's exact tests were used to evaluate the relationships between endpoints and categorical variables. Kaplan–Meier analysis was conducted to evaluate the variables affecting survival. Univariate and multivariate Cox's proportional hazard regression analyzes were used to evaluate the associations between BDNF levels and cardiovascular mortality. A p-value <0.05 was considered as statistically significant.

Results

Demographic and clinical specifications of the study population are shown in Table 1. No difference between the control and patient groups was identified with respect to age and sex. The majority of patients with HF were male (94, 58%). The average age of the patient group was 67.60±11.45 years, and the average age of the control group was 66.28±11.30 years. In the patient group, 69% had hypertension, 48% had diabetes mellitus, 64% had CAD, 41% had chronic atrial fibrillation, and 20% had chronic renal failure. Furthermore, the laboratory parameters revealed that the patient group had high levels of creatinine, potassium, glucose, C-reactive protein (CRP), and troponin, but low levels of hemoglobin and albumin, compared with the control group. The NT-pro-BNP serum levels of patients with HF were higher, whereas the BDNF values were lower than those of the control group (NT-pro-BNP: 5010±851 pg/mL vs. 33±11 pg/mL, p<0.001 and BDNF: 8.64±1.12 ng/mL vs. 17.58±4.51 ng/mL, p<0.001). Among patients with HF, 13% (21 patients) had an intracardiac defibrillator. Upon echocardiographic investigation, the average EF of the patient group was found to be 27.8%, whereas the average EF of the control group was 64%. The pulmonary artery systolic pressure (PASP) and left ventricular mass index of the patient group were higher than those of the control group (Table 1).

When patients with HF were classified among themselves according to functional capacity (NYHA I–II vs. NYHA III), no difference was observed between their EF, PASP, CRP, and left ventricular mass index levels. However, the values of NT-pro-BNP and troponin were determined to be higher, and the values of BDNF were determined to be lower in patients with functional capacity NYHA III than in patients with NYHA II (Table 2) [NT-pro-BNP: 5006±844 pg/mL vs. 4339±642 pg/mL, p<0.001; troponin: 0.03 mg/dL (0.04–0.12 mg/dL) vs. 0.03 mg/dL (0.02–0.045 mg/dL), p=0.002; and BDNF 9.77 ng/mL (8.73–9.93 ng/mL) vs. 10.22 ng/mL (9.87–10.50 ng/mL), p<0.001, respectively].

Serum BDNF levels predict adverse outcomes

During a median follow-up of 29.4 months, there were 147 adverse events, including 49 cardiac deaths and 98 rehospitalizations due to worsening of HF. The variables to predict adverse outcomes were identified by logistic regression using univariate and multivariate analyzes.

To investigate the prognostic factors that affected the survival time of patients with HF, the variables for which the prognostic significance had been previously proven and the BDNF levels were analyzed by Cox regression model. High NT-pro-BNP levels [odds ratio (OR)=1.04, p<0.001] and low BDNF levels (OR=0.17, p=0.002) were determined as independent indicators of survival time. Furthermore, for the predictors that affected the time elapsed to hospitalization due to HF, the variables for which the prognostic significance had been previously proven and the BDNF levels were analyzed by Cox regression model. High NT-pro-BNP levels (OR=1.07, p<0.001) and low BDNF levels (OR=0.702, p=0.010) were determined as effective independent indicators of the length of time until rehospitalization (Tables 3 and 4).

The receiver operating characteristic curves of serum BDNF values for the prediction of all cardiac deaths are shown in Figure 2. Serum BDNF level of 9.10 ng/mL was defined as the optimal cutoff point for determining the adverse outcomes, exhibiting 88% sensitivity and 87% specificity. The area under the curve of the serum BDNF levels for the prediction of adverse events was 0.837 [95% confidence interval (CI): 0.735–0.938; p<0.001].

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Table 1. Baseline demographic and clinical characteristics of the patient and control groups

	HF n=160 (%)	Control n=50 (%)	*P*-value
Age, year (mean±SD)	67.60±11.45	66.28±11.30	
Male, n (%)	94 (58)	24 (48)	0.181
Body mass index (kg/m^2)	29.95±6.59	29.84±6.29	0.918
Smoking, n (%)	65 (40)	26 (52)	0.157
Ischemic heart disease, n (%)	103 (64)	0 (0)	**<0.001**
Hypertension, n (%)	111 (69)	11 (22)	**<0.001**
Diabetes mellitus, n (%)	78 (48)	10 (20)	**<0.001**
CRD (eGFR ≤45), n (%)	32 (20)	0 (0)	**<0.001**
Atrial fibrillation, n (%)	66 (41)	0 (0)	**<0.001**
Beta blockers, n (%)	129 (80)	11 (22)	**<0.001**
ACE inhibitors/ARB, n (%)	113 (70)	8 (16)	**<0.001**
Spironolactone, n (%)	62 (38)	0 (0)	**<0.001**
Digoxin, n (%)	37 (23)	0 (0)	**<0.001**
ICD, n (%)	21 (13)	0 (0)	**<0.001**
Systolic blood pressure (mm Hg)	124.43±23.66	132.00±19.89	**0.039**
Heart rate (min)	91.34±25.62	85.18±18.44	0.088
LVEF (%)	27.89±6.89	64.62±8.85	<0.001
PASP (mm Hg)	49.89±21.14	24.98±7.93	<0.001
Creatinine, mg/dL	1.46±0.53	0.84±0.33	<0.001
Sodium, mEq/L	138.05±4.68	139.53±3.97	0.057
Potassium, mEq/L	4.62±0.78	4.71±0.54	0.461
Hemoglobin, g/dL	12.32±2.17	12.65±2.12	0.383
Glucose, mg/dL	144.30±51.63	90.62±8.21	<0.001
Albumin, g/dL	3.99±0.50	4.03±0.62	0.622
CRP (mg/dL)	14.4±5.72	1.84±0.35	<0.001
Troponin (mg/dL)	0.262±0.118	0.042±0.015	<0.001
NT-pro-BNP (pg/mL)	5010±851	33±11	<0.001
BDNF (ng/mL)	8.64±1.12	17.58±4.51	<0001
Left ventricular mass index (g/m^2)	149.18±29.90	88.23±11.61	<0.001

HF - heart failure; SD - standard deviation; CRD - chronic renal disease; eGFR - estimated glomerular filtration rate; ACE - angiotensin-converting-enzyme; ARB - angiotensin II receptor blocker; ICD - implantable cardioverter defibrillators; LVEF - left ventricular ejection fraction; PASP - pulmonary artery systolic pressure; CRP - C-reactive protein; NT-pro-BNP - N-terminal pro-brain-type natriuretic peptide; BDNF - brain-derived neurotrophic factor

Table 2. Comparison of the heart failure group according to functional capacity

	NYHA I-II (n=52)	NYHA III (n=108)	*P*-value
LVEF (%)	30 (25-35)	30 (24-35)	0.182
PASP (mm Hg)	49±22	43±13	0.119
CRP (mg/dL)	8 (3.75-17.75)	10 (6-32)	0.131
Troponin (mg/dL)	0.03 (0.02-0.045)	0.03 (0.04-0.12)	0.002
NT Pro-BNP (pg/mL)	4339±642	5006±844	<0.001
BDNF (ng/mL)	10.22 (9.87-10.50)	9.77 (8.73-9.93)	<0.001
Left ventricular mass index (g/m^2)	145±38	149±36	0.502

Data shown are median (interquartile range) or mean±standard deviation.
LVEF - left ventricular ejection fraction; PASP - pulmonary artery systolic pressure; CRP - C-reactive protein; NT-pro-BNP - N-terminal pro-brain-type natriuretic peptide; BDNF - brain-derived neurotrophic factor; NYHA - New York Heart Association

Table 3. Univariate Cox's proportional hazard regression analysis of predictors of cardiovascular mortality and rehospitalization in patients with heart failure

	Predictors of all cardiac death			Predictors of HF rehospitalization		
Variable	**OR**	**95% CI**	***P*-value**	**OR**	**95% CI**	***P*-value**
Age	1.032	0.999-1.065	0.058	1.025	1.001-1.050	0.037
Gender	1.522	0.743-3.119	0.251	0.763	0.468-1.242	0.277
CAD	0.741	0.376-1.459	0.386	1.241	0.774-1.990	0.370
Hypertension	0.813	0.397-1.666	0.572	1.215	0.730-2.021	0.454
DM	1.063	0.547-2.063	0.857	1.158	0.724-1.852	0.540
AF	1.448	0.708-2.960	0.310	1.106	0.678-1.805	0.685
LVEF	0.098	0.000-19.889	0.392	0.127	0.003-5.573	0.285
PASP (mm Hg)	1.011	0.992-1.031	0.251	0.999	0.982-1.015	0.862
Sodium	0.925	0.860-0.995	**0.036**	0.956	0.913-1.001	**0.054**
Troponin	1.872	1.136-3.086	**0.014**	1.594	1.035-2.456	**0.034**
NT-ProBNP	1.025	1.011-1.039	**<0.001**	1.001	1.000-1.001	**<0.001**
BDNF	0.601	0.522-0.692	**<0.001**	0.770	0.705-0.841	**<0.001**
NYHA	0.743	0.365-1.515	0.414	1.232	0.750-2.024	0.410
eGFR	0.988	0.977-0.999	**0.028**	0.993	0.985-1.001	**0.086**

CAD - coronary artery disease; DM - diabetes mellitus; AF - atrial fibrillation; LVEF - left ventricular ejection fraction; PASP - pulmonary artery systolic pressure; NT-pro-BNP - N-terminal pro-brain-type natriuretic peptide; BDNF - brain-derived neurotrophic factor; NYHA - New York Heart Association; eGFR - estimated glomerular filtration rate

Table 4. Multiple Cox's proportional hazard regression analysis of predictors of cardiovascular mortality and rehospitalization in patients with systolic heart failure

	Predictors of all cardiac death			Predictors of HF rehospitalization		
Variable	**OR**	**95% CI**	***P*-value**	**OR**	**95% CI**	***P*-value**
Age	0.979	0.924-1.038	0.486	0.980	0.956-1.004	0.101
BDNF	0.170	0.054-0.533	**0.002**	0.702	0.538-0.917	**0.010**
NT-pro-BNP	1.041	1.019-1.063	**<0.001**	1.071	1.012-1.134	**<0.001**
Troponin	2.939	0.260-33.206	0.383	1.266	0.951-1.684	0.106
eGFR	0.993	0.974-1.013	0.476	0.997	0.989-1.006	0.529
Sodium	0.898	0.750-1.075	0.241	0.956	0.904-1.011	0.112

OR - odds ratio; CI - confidence interval; BDNF - brain-derived neurotrophic factor; NT-pro-BNP - N-terminal pro-brain-type natriuretic peptide; eGFR - estimated glomerular filtration rate

Spearman correlation analysis was performed to investigate the relationship between NT-pro-BNP and BDNF levels, which was found to be statistically significant ($p<0.001$, $r=-0.723$). Thus, as BDNF level decreased, an increase in NT-pro-BNP level was observed (Fig. 3).

Discussion

In the present study, the prognostic significance of the BDNF values was investigated in patients with severe left ventricular systolic dysfunction (LVEF ≤35%) of mildly symptomatic (NYHA I–II) and severely symptomatic (NYHA III) individuals and in the control group without any known history of cardiac disease. The main findings of our study are as follows:

1. The BDNF values of patients with HF were determined to be lower, and the NT-pro-BNP values were determined to be higher than those of the control group (BDNF: 8.64±1.12 ng/mL vs. 17.58±4.51 ng/mL, $p<0.001$; NT-pro-BNP: 5010±851 pg/mL vs. 33±11 pg/mL, $p<0.001$, respectively).
2. When patients with HF were compared according to their functional capacity, the BDNF levels of the severely symptomatic (NYHA III) patients were lower than those of the mildly symptomatic (NYHA I–II) patients [BDNF: 9.77 ng/mL

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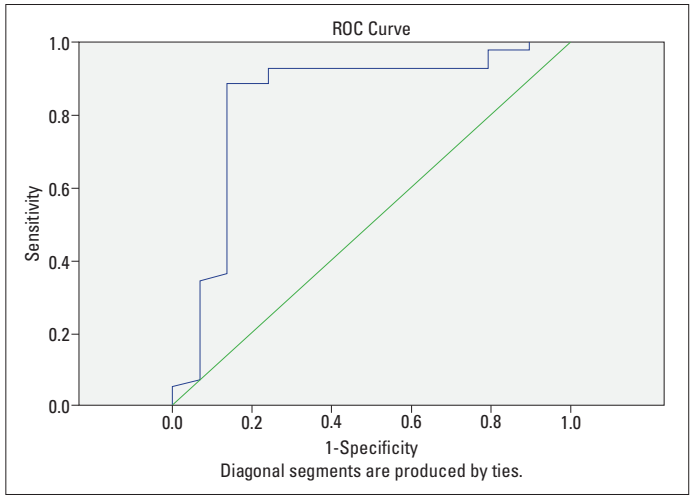

Figure 2. Predictive ability of serum brain-derived neurotropic factor levels for all cardiac death

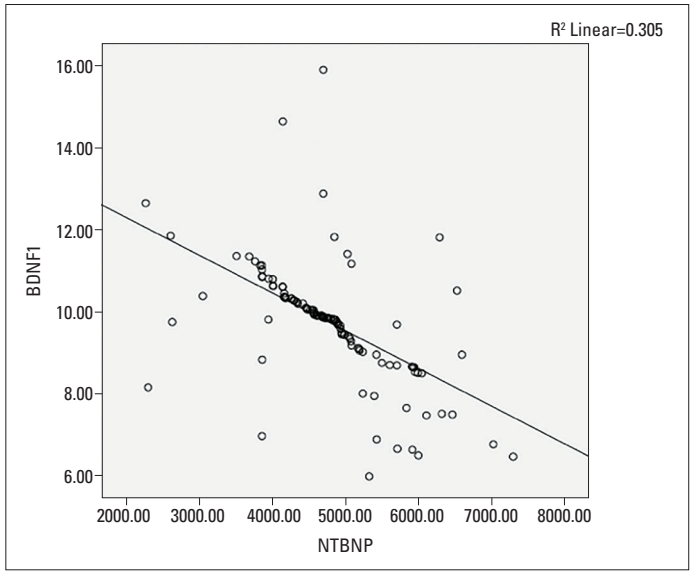

Figure 3. Spearman correlation analysis of NT-pro-BNP and BDNF levels

(8.73–9.93 ng/mL) vs. 10.22 ng/mL (9.87–10.50 ng/mL), p<0.001, respectively].

3. In univariate and multivariate analyzes, a correlation was found between low serum BDNF levels, rehospitalizations, and cardiac deaths (cardiac deaths, OR=0.17, p=0.002; rehospitalizations, OR=0.702, p=0.010).

Neurotrophins from the dimeric polypeptide-structured growth factor family affect neuron growth, proliferation, and function; provide synapse stabilization; control synaptic function and synaptic plasticity; and regulate axon and dendritic branching (6). It has been determined that BDNF is synthesized from non-neuronal cells in the central nervous system, peripheral vascular endothelial cells, lymphocytes, thrombocytes, leukocytes, and monocytes and from the T and B cells (8). BDNF specifically binds to the tropomyosin-related kinase receptor B (TrkB) and activates many intracellular signaling pathways. Accumulating evidence suggests that BDNF is also required for the development of the cardiovascular system. It has been reported that the transcriptional activation of TrkB is crucial for coronary vessel development (23). The previous studies have revealed that BDNF acts on the endothelial cells and promotes neovascularization in response to hypoxic stimuli via the Akt pathway (24, 25). However, it remains unclear whether BDNF is involved in the pathophysiology of adult cardiac diseases, such as myocardial infarction and HF (14-17).

The relationship between BDNF and CAD has been investigated in various studies, and it has been suggested that BDNF release increases in the ischemic heart and protects the heart against ischemic damage (26). Furthermore, it has been suggested that BDNF may play a role in coronary atherosclerosis and may be associated with major cardiac events and cardiac mortality (14). However, in the present study, there was no significant difference in serum BDNF levels compared with patients without CAD, even though documented CAD (coronary artery bypass surgery or percutaneous coronary intervention) was present in 103 patients with HF.

The relationship between HF and serum BDNF levels has been evaluated in several recent studies. A study performed by Fukushima et al. (16) in a small number (n=58) of patients with HF showed that low serum BDNF levels have been associated with adverse events, as in our study. In their study, patients with both reduced and preserved ejection fraction HF were included, and a small number of adverse events (8 cardiac deaths and 11 rehospitalizations) were observed in a median follow-up of 20.3 months. In our study, only patients with HF and reduced LVEF (≤35%) were included, and 147 adverse events (49 cardiac deaths and 98 hospitalizations) were observed in 160 patients who were admitted to the study for a mean follow-up of 29.4 months. In this study (16, 17), cardiac-induced deaths and rehospitalizations were considered together as the only endpoint due to the small number of patients. Our study was a prospective study in which mildly symptomatic patients, severely symptomatic patients, and healthy individuals were included, and primary endpoints (cardiac death and hospitalization) were evaluated individually. In addition, by retrospectively evaluating the results by Kadowaki et al. (17), serum BDNF levels in patients with acute and chronic and systolic and diastolic HF are found to be significantly lower in patients with congestive HF than in the control group, and low BDNF level was an independent risk factor for cardiac events. This study consisted only of patients with chronic systolic HF. Takashio et al. reported that plasma BDNF levels are significantly lower in patients with HF than in those without HF, and low BDNF levels correlate with the severity, as evaluated in the NYHA functional class of HF (14).

The exact reason for the decrease in serum BDNF levels of patients with HF is not known. However, among the hypotheses, it is suggested that the reduction in skeletal muscle mass in patients with HF may be one of the reasons for reducing BDNF secretion, as BDNF is also released from the skeletal muscles

(27, 28). Moreover, sympathetic hyperactivity occurs in patients with HF, suggesting that BDNF levels may be reduced in this condition (29-31).

Study limitations

The present study had certain limitations. First, only basal BDNF levels were measured, and no recurrent measurements were made in clinical follow-ups. Second, although the present study was a prospective study, the correlation of patients with other factors affecting serum BDNF levels, such as depressive symptom score, anxiety, stress, and drug dependency, had not been evaluated (32, 33). The use of BDNF as brain natriuretic peptide in patients with HF requires a greater number of patients and longer follow-up periods.

Conclusion

As shown by our study results, serum BDNF levels may be used as prognostic and independent biomarkers in patients with severe left ventricular dysfunction. Furthermore, BDNF levels showed close prognostic correlation with NT-pro-BNP levels.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

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