Biochemical and Biophysical Research Communications 415 (2011) 99–103

Contents lists available at SciVerse ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

Association of plasma brain-derived neurotrophic factor and cardiovascular risk factors and prognosis in angina pectoris

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ARTICLE INFO

Article history:
Received 4 October 2011
Available online 12 October 2011

Keywords:
Brain-derived neurotrophic factor
Angina pectoris
Coronary events
Risk factors

ABSTRACT

Background: Collateral circulation can protect and preserve the myocardium against episodes of ischemia and reduce cardiovascular events. Brain-derived neurotrophic factor (BDNF) is an angiogenic regulator promoting angiogenesis. We compared the association of plasma levels of BDNF and C-reactive protein, an established marker, and risk factors of cardiovascular dysfunction and prognosis in patients with angina pectoris.

Methods: We enrolled 885 patients with angina pectoris. Plasma BDNF and CRP were measured by ELISA. Patients were prospectively followed for a median of 48 months (interquartile range 37–59 months), and information on further coronary events and mortality was collected.

Results: Multiple risk factors for cardiovascular disease were independent determinants of low plasma BDNF level in patients with angina pectoris. Plasma BDNF was inversely associated with levels of triglycerides and low-density lipoprotein cholesterol, presence of diabetes mellitus, fibrinogen level, male sex and age and positively with high-density lipoprotein cholesterol level and platelet count. During follow-up, 15.2% of patients experienced a major coronary event (MCE), and 10.5% died. The plasma BDNF level was an independent predictor of 4-year MCE (adjusted hazard ratio = 1.25 with 95% confidence interval 1.10–1.41, $P < 0.01$ for each unit increase in the natural logarithm of the BDNF level) and of 4-year mortality (adjusted hazard ratio = 1.29, 95% confidence interval 1.11–1.47, $P < 0.01$).

Conclusion: Multiple cardiovascular risk factors are associated with plasma BDNF level in patients with angina pectoris, and low plasma BDNF may be associated with future coronary events and mortality in these patients.

1. Introduction

Collateral circulation can protect and preserve the myocardium against episodes of ischemia, enhance residual myocardial contractility, and reduce angina symptoms and cardiovascular events [1–3]. Angiogenesis plays an important role in collateral vessel formation.

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family of growth factors and promotes survival, differentiation, and maintenance of neurons in the peripheral and central nervous systems [4]. BDNF also plays a role in the cardiovascular system. BDNF functions as an angiogenic regulator to promote angiogenesis. Embryonic BDNF deficiency severely impairs the development of intramyocardial vessels and can lead to cardiac hypocontractility [5]. BDNF enhances vascular flow and regulates revascularization of ischemic tissues [6]. It can improve angiogenesis and left-ventricular function in the ischemic myocardium [7].

BDNF is present outside of the central nervous system and circulates systemically [8,9]. Platelets appear to bind, store and release BDNF into plasma [10]. Decreased plasma BDNF level was found in patients with acute coronary syndromes [11]. Diabetes mellitus is a major risk factor and risk-equivalent of coronary artery disease [12], and plasma BDNF was found decreased in patients with diabetes mellitus [13]. Moreover, low plasma BDNF levels may be linked to increased mortality in elderly women [14]. However, whether this biomarker can provide prognostic information for coronary artery disease (CAD) is unknown.

Abbreviations: CAD, coronary artery disease; CRP, high-sensitivity C-reactive protein; BDNF, brain-derived neurotrophic factor; TG, triglycerides; LDL, low-density lipoprotein; HDL, high-density lipoprotein; MCE, major coronary event.

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doi:10.1016/j.bbrc.2011.10.020

We compared the association of levels of plasma BDNF and C-reactive protein (CRP), an established prognostic marker of CAD, and risk factors of cardiovascular dysfunction and prognosis in patients with angina pectoris.

2. Methods

2.1. Patients

We examined 885 patients with angina pectoris from Qilu Hospital, Shandong University. All patients had >50% stenotic lesions in at least one major coronary vessel as determined by coronary angiography. The unstable angina pectoris (UAP) group consisted of 575 (64.9%) patients who had anginal episodes at rest without a significant increase in cardiac troponin levels (according to the ACC/AHA 2007 guidelines for the management of patients with unstable angina). The stable angina pectoris (SAP) group consisted of 310 (35.1%) patients with typical symptoms of angina during exertion or positive treadmill exercise testing but no episodes of angina at rest. T2DM was defined as a previous diagnosis of the disease, history of antidiabetic medications, fasting plasma glucose (FPG) >7.0 mmol/L on at least two occasions or positive results of a standard oral glucose tolerance test. Of these T2DM patients, 228 (61.3%) had T2DM before admission; the remaining 144 (38.7%) were diagnosed for the first time during hospitalization. We excluded patients with myocardial infarction within the preceding 2 months or with severe right-heart failure or noncardiac diseases likely to cause death within 1 year. The control group consisted of 543 healthy subjects (age: 62 ± 9.3 years and gender ratio (M/F): 65.7%/34.3%), screened during routine physical check-up during the same time. There were no significant differences between the patients and control groups on age and gender (all $P > 0.05$). Because we could not perform coronary angiography to rule out asymptomatic CAD in control patients, the inclusion criteria were as described [15]. No subject had a mental disorder or was taking antidepressant drugs or tranquilizers.

2.2. Measurement of plasma BDNF levels

Blood samples were obtained between 7:30 and 8:00, within 24 h of hospitalization for patients. Blood samples were put in tubes containing EDTA (pH 7.5) and immediately centrifuged at 3000 rpm for 10 min at 4 °C, then plasma samples were stored at −80 °C. Plasma BDNF and hsCRP concentrations were measured by use of ELISA kits (BDNF Emax® ImmunoAssay System, Promega, USA; Human hs-CRP ELISA kit, USCNLIFE, USA). The intra- and interassay coefficients of variation were <10%.

2.3. Follow-up and clinical end points

The patients were followed from the time of the first angiography in 2006–2008 and through to 2011. The end points were major coronary events (MCEs) and all-cause mortality. MCE included fatal or nonfatal acute myocardial infarction, sudden cardiac death, and sudden death (International Statistical Classification of Disease Tenth Revision [ICD-10] codes I46 and R96 for sudden cardiac death and sudden death, respectively). Myocardial infarction was classified according to the diagnostic criteria of the revised definition published in 2000 [16]. Patients with events occurring within 72 h of surgery (usually coronary artery bypass surgery) or angioplasty were excluded from analyses.

2.4. Statistical analysis

Data are presented as mean ± SD, median (interquartile range [IQR]) and or number (percentage). We performed linear regression analysis of factors associated with plasma BDNF level. Kaplan–Meier curves were used for unadjusted cumulative survival (MCEs and all-cause mortality) according to tertiles of BDNF levels. The predictive value of plasma BDNF level was assessed by Cox regression analysis. Plasma BDNF was entered into the model after logarithmic transformation. The proportional hazards assumption was checked by the method of Grambsch and Themeau [17] and was fulfilled in all cases for Cox proportional hazards models. The incremental prognostic value of biomarkers was tested by calculation of the area under the receiver operating characteristic curve with a follow-up time of 48 months. Multivariable models with conventional risk markers were compared with models that also included BDNF or CRP. The discriminatory power of the model for MCE and mortality with and without BDNF was assessed by calculating the *c* statistic in the Cox proportional hazards model and integrated discrimination improvement (IDI) as described [18]. All analyses involved use of S-PLUS (Insightful Corp., Seattle, WA). A two-sided $P < 0.05$ was considered statistically significant. All analyses were performed in a blinded fashion.

3. Results

3.1. Association of risk factors of CAD and plasma BDNF level

Table 1 shows the characteristics of the patients. Linear regression analysis revealed elderly age, male sex, presence of diabetes, elevated TG and LDL levels, reduced HDL level, elevated fibrinogen level and reduced platelet count independently associated with low BDNF level (Table 2).

3.2. Plasma BDNF level and MCE

During a median follow-up of 48 months (IQR 37–59 months), 15.2% of patients experienced an MCE. The low tertile of BDNF level was associated with a significantly higher probability of MCE than the middle and high tertiles (Fig. 1A). The plasma BDNF level was an independent predictor of 4-year MCE (unadjusted hazard ratio (HR) was 1.41 with 95% confidence interval 1.2–1.53 and the multivariable HR was 1.25 (1.10–1.41); both $P < 0.01$ for each unit increase in the natural logarithm of the BDNF level). The adjusted HR for CRP level was 1.22 (1.11–1.39) (Table 3).

3.3. Plasma BDNF level and all-cause mortality

A total of 10.5% of patients died during follow-up. The low tertile of BDNF level was associated with a significantly higher probability of all-cause mortality than the middle and high tertiles (Fig. 1B). The plasma BDNF level was an independent predictor of 4-year mortality (unadjusted HR was 1.37 (1.22–1.49) and the multivariable HR was 1.29 (1.11–1.47); both $P < 0.01$ for each unit increase in the natural logarithm of the BDNF level). Similarly, CRP level independently predicted all-cause mortality in the multivariable model (Table 3).

3.4. Evaluation of survival models

The multivariable model without BDNF yielded values for the area under the receiver operating characteristics curve of 0.561 and 0.622 for MCE and all-cause mortality, respectively. Inclusion of BDNF increased areas by 0.070 and 0.073 (both $P < 0.05$), respectively. CRP level did not increase areas for either of the end points (all $P > 0.05$).

For MCE and mortality, the *c* statistic of the model without BDNF was 0.572 and 0.608; adding BDNF increased the *c* statistic to 0.583 and 0.616. The inclusion of BDNF in the multivariable

Table 1
Baseline characteristics of patients with angina pectoris ($n = 885$).

Characteristic	Value	Characteristic	Value
Age (year)	62.1 ± 11.2	Coronary Gesini score	52.9 ± 38.6
Sex, M/F (%)	68.5/31.5	Number of diseased vessels	2.3 ± 0.9
Body mass index (kg/m^2)	24.6 ± 3.6	C-reactive protein (mg/L)	2.89 ± 1.05
Systolic blood pressure (mm Hg)	130 ± 19	Fibrinogen	3.77 ± 1.31
Diastolic blood pressure (mm Hg)	75 ± 12	Platelet counts	233.73 ± 74.64
Total cholesterol (mmol/L)	4.8 ± 1.2		
Triglycerides (mmol/L)	1.7 ± 1.0	Medication use, *n* (%)	
High-density lipoprotein cholesterol (mmol/L)	1.2 ± 0.32	Aspirin	882 (99.7)
Low-density lipoprotein cholesterol (mmol/L)	3.0 ± 0.8	Statins	860 (97.2)
Glucose (mmol/L)	6.0 ± 1.2	Beta blockers	857 (96.8)
Left-ventricular ejection fraction (%)	60 ± 12	Angiotensin-converting enzyme inhibitors	669 (75.6)
Diabetes mellitus (%)	372 (42.0)		
Hypertensive agents (%)	573 (64.7)	Clinical end points during follow-up	
Smoking (%)	374 (42.2)	Major coronary event	135 (15.2)
Atrial fibrillation (%)	57 (6.4)	All-cause mortality	93 (10.5)

Table 2
Linear regression analysis of cardiovascular risk factor predictors of plasma level of brain-derived neurotrophic factor.

Variable	Standardized regression coefficient	*P* value
Age	−0.162	0.005
Male sex	−0.161	0.027
Diabetes mellitus	−0.104	0.048
TG level	−0.260	0.039
LDL level	−0.565	0.016
HDL level	0.197	0.030
Fibrinogen level	−0.237	0.007
Platelet count	0.158	0.017

TG, triglycerides, LDL, low-density lipoprotein, HDL, high-density lipoprotein.

model was associated with a significant improvement in discriminatory power of the model for predicting 4-year MCE (absolute IDI 0.007, relative IDI 5.6%; $P = 0.025$) and mortality (absolute IDI 0.009, relative IDI 6.2%; $P = 0.021$). CRP level did not increase discriminatory power of the model.

4. Discussion

We compared the association of plasma levels of BDNF and CRP and cardiovascular risk factors and prognosis in patients with angina pectoris. Lipid levels, presence of diabetes mellitus, fibrinogen level, male sex, elderly age and reduced platelet count were independent determinants of plasma BDNF level in patients with angina pectoris. Low plasma BDNF was a predictor of adverse prognosis (MCE and all-cause mortality) in patients with angina pectoris. Moreover, plasma BDNF seemed to provide more prognostic information than CRP, the established marker.

The specific source of plasma BDNF is unknown. BDNF is in the central and peripheral nervous system and in heart, endothelial cells, lymphocytes, muscle and liver [5,9,19–21]. However, plasma BDNF has a half-life of less than 60 min after intravenous BDNF injection [22]. Platelets appear to bind, store and release BDNF into plasma [10]. Under normal circumstances, the difference between plasma and serum BDNF levels is ~200-fold [10,23,24]. Platelets regulate new blood vessel growth through numerous stimulators and inhibitors of angiogenesis by several pathways, including differential exocytosis of angiogenesis regulators [25]. We found plasma BDNF level positively associated with platelet count in patients with angina pectoris. Lughetti et al. found platelet count the most important predictor of plasma BDNF concentration in children and adolescents [26]. The positive association of plasma BDNF level and platelet count suggests that low plasma BDNF concentration in patients with angina pectoris may be mainly explained by platelet release.

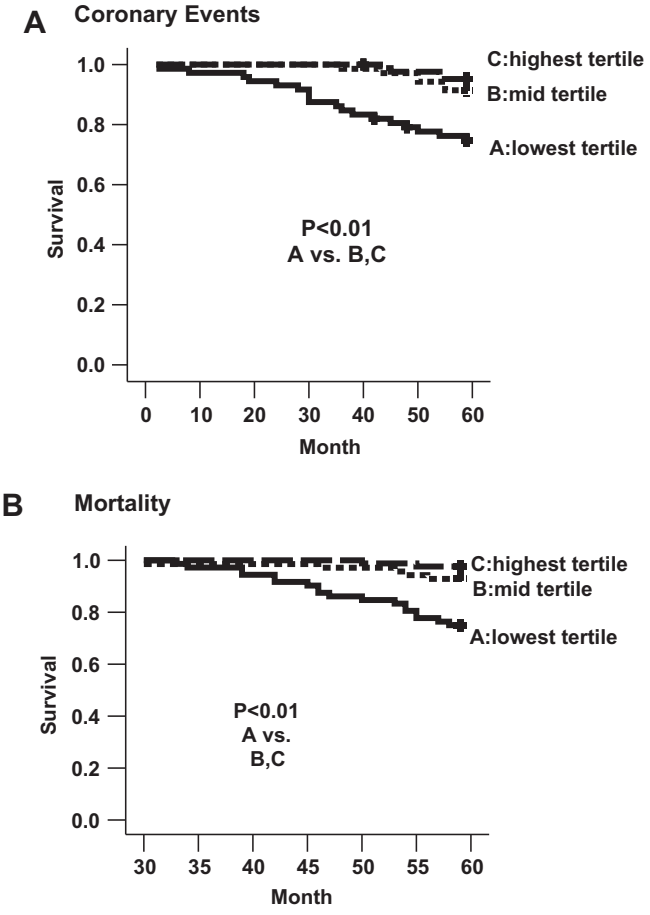

Fig. 1. Kaplan–Meier curves showing unadjusted cumulative incidence of major coronary events and all-cause mortality by tertiles of level of brain-derived neurotropic factor.

We found plasma BDNF levels decreased with increasing age and male sex, as was reported previously [27]. As well, low plasma BDNF level was associated with increased TG and LDL levels, decreased HDL cholesterol level, and presence of diabetes mellitus. Plasma BDNF level has been found related to a lipid profile in women with obesity [28] and was significantly lower in patients with type 2 diabetes mellitus than controls [13]. We found plasma BDNF level negatively associated with fibrinogen level in patients with angina pectoris. Fibrinogen, as with BDNF, is a major storage protein of platelet alpha-granules and is delivered to alpha-granules

Table 3
Comparison of plasma levels of C-reactive protein and brain-derived neurotrophic factor (BDNF) and risk of major coronary events or all-cause mortality.

	Hazard ratio (95% CI)			
	Model I, simple[a]		Model II, multivariable[b]	
	Value	*P* value	Value	*P* value
Major coronary event				
BDNF	1.41 (1.27–1.53)	<0.01	1.25 (1.10–1.41)	<0.01
C-reactive protein	1.35 (1.18–1.45)	<0.01	1.22 (1.11–1.39)	<0.01
All-cause mortality				
BDNF	1.37 (1.22–1.49)	<0.01	1.29 (1.11–1.47)	<0.01
C-reactive protein	1.40 (1.26–1.55)	<0.01	1.21 (1.09–1.40)	<0.01

[a] Adjustment for age and sex.
[b] Adjustment for all variables of Table 1.

by endocytosis [29]. The exact reason for the association of decreased plasma BDNF levels and these factors is unclear but may be associated with the level of BDNF release from platelets in inflammatory states.

We found plasma BDNF level a predictor of adverse prognosis (MCE and all-cause mortality) in patients with angina pectoris. Data from the Danish National Register of Patients also showed a significantly increased risk of all-cause mortality in elderly women with low plasma BDNF level [14]. Low plasma BDNF level may affect angiogenesis and thus the development of collateral vessels in patients with angina pectoris. More than 15 growth factors stimulate collateral growth and angiogenesis [30,31]. Plasma elevation in BDNF can have a direct chemotactic action on subsets of bone-marrow–derived Sca-1+CD11b+ cells expressing TrkB, promoting their mobilization from marrow to peripheral circulation [32]. Hematopoietic cells contribute to revascularization of ischemic or regenerating tissues by releasing angiogenic factors, thereby supporting the assembly of new vessels [33–44].

Limitations of our study include the single measurement of biomarkers, which may have led to underestimation of the true strength of the association by so-called regression dilution bias [45]. Another limitation is the absence of in vivo and in vitro functional studies.

In conclusion, we found cardiovascular risk factors independently associated with plasma BDNF level in patients with angina pectoris. As well, plasma BDNF level predicted long-term prognosis independently of traditional CAD risk factors. The biological mechanism determining plasma BDNF levels and their pathophysiological implications require clarification. Plasma BDNF may be a useful marker for improving treatment or a potential target for novel therapeutic strategies in CAD.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

H.J. participated in the design of the study, measurement of plasma BDNF and CRP level, follow-up, and statistical analysis, and drafted the manuscript. Z.Y.C. and Y.Z. contributed to the design and coordination of the study, statistical analysis, interpretation of findings and drafting the manuscript. Y.L. participated in the design of the study, measurement of plasma BDNF level and follow-up. All authors read and approved the final manuscript.

Acknowledgments

This study was supported by the National Natural Science Foundation of China (30725020), the State Program of National Natural Science Foundation of China for Innovative Research Group (No. 81021001) and the Independent Innovation Foundation of Shandong University (2011DX001).

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