Circulating brain-derived neurotrophic factor dysregulation and its linkage with lipid level, stenosis degree, and inflammatory cytokines in coronary heart disease

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Abstract

Background: Brain-derived neurotrophic factor (BDNF) regulates the lipid metabolism, atherosclerosis plaque formation, and inflammatory process, while the study about its clinical role in coronary heart disease (CHD) is few. The present study intended to explore the expression of BDNF and its relationship with stenosis, inflammation, and adhesion molecules in CHD patients.

Methods: After serum samples were obtained from 207 CHD patients, BDNF, tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, IL-6, IL-8, IL-17A, vascular cell adhesion molecule-1 (VCAM-1), and intercellular adhesion molecule-1 (ICAM-1) levels were determined using ELISA. Then, the BDNF level was also examined in 40 disease controls (DCs) and 40 healthy controls (HCs), separately.

Results: BDNF was lower in CHD patients than in DCs and HCs (median (95% confidential interval) value: 5.6 (3.5–9.6) ng/mL vs. 10.7 (6.1–17.0) ng/mL and 12.6 (9.4–18.2) ng/mL, both \(p<0.001\)). BDNF could well distinguish CHD patients from DCs (area under the curve [AUC]: 0.739) and HCs (AUC: 0.857). BDNF was negatively associated with triglyceride (\(p=0.014\)), total cholesterol (\(p=0.037\)), and low-density lipoprotein cholesterol (\(p=0.008\)). BDNF was negatively associated with CRP (\(p<0.001\)), TNF-α (\(p<0.001\)), IL-1β (\(p=0.008\)), and IL-8 (\(p<0.001\)). BDNF was negatively related to VCAM-1 (\(p<0.001\)) and ICAM-1 (\(p=0.003\)). BDNF was negatively linked with the Gensini score (\(p<0.001\)).

Conclusion: BDNF reflects the lipid dysregulation, inflammatory status, and stenosis degree in CHD patients.

KEYWORDS

BDNF, coronary heart disease, inflammation, lipid, stenosis

Feng Xia and Qingrong Zeng contributed equally to this work.

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Coronary heart disease (CHD) ranks as the most prevalent cardiovascular disease, which is characterized by stenosis or blockage in the coronary artery. The prevalence of CHD is high among the general population ranging from 1.29% to 9.2%. Recently, even though the ischemia improvement and antiplatelet drugs (such as the beta receptor-blocking agent, statins, and nitrates) have been widely applied in treating CHD patients, the disease continues to progress; besides, their long-term survival is unsatisfied with a 5 years survival rate ranging from 49.3% to 82.9%. Therefore, it is essential to develop the potential biomarker to monitor the disease progression and predict the survival of CHD patients, which might assist the clinicians to stratify CHD patients and individualize them, thus further improving the prognosis of CHD patients.

Brain-derived neurotrophic factor (BDNF) expressed in the mammalian brain widely may regulate neuronal survival, morphogenesis, and plasticity in multiple pathways. Recently, BDNF has been widely reported to be involved in regulating several biological processes associated with the onset of CHD such as the abnormal lipid metabolism, formation of atherosclerosis plaque, inflammatory processes associated with the onset of CHD such as abnormal lipid metabolism, and adhesion molecules production. For instance, one study shows that the production of BDNF might enhance lipid metabolism; another study discloses that the activation of BDNF could help to confer protection against atherosclerosis; apart from that, BDNF reduces the inflammation induced by the oxygen-glucose deprivation and reoxygenation (OGD/R). Based on what is mentioned above, we hypothesized that the BDNF might be a protective role in the pathogenesis of CHD, and its measurement may be useful for the clinical management of CHD. Therefore, the current study aimed to explore the expression of BDNF and its relationship with stenosis, inflammation, and adhesion molecules in CHD patients.

2 | METHODS

2.1 | Subjects

From February 2020 to September 2021, this study serially recruited 207 patients with CHD confirmed by coronary angiography. The enrollment criteria were as follows: (A) diagnosed as CHD by coronary angiography; (B) over 18 years old; and (C) volunteered to provide peripheral blood samples. The exclusion criteria were as follows: (A) had a prior history of cardiac, lung, or vascular surgery; (B) concomitant with a solid tumor, hematologic malignancy, autoimmune disease, or active infection; and (C) pregnant or breastfeeding female patients. During the same period, this study enrolled 40 patients as disease controls (DCs), who came to the hospital for chest pain of unknown cause or suspected CHD symptoms and were diagnosed as non-CHD by coronary angiography. The eligible DCs were matched for age and gender with CHD patients. Besides, a total of 40 healthy subjects who had matched age and gender were recruited as healthy controls (HCs). The study was permitted by the ethics committee. All subjects signed the written informed consent form.

2.2 | Data collection and sample detection

Clinical characteristics were collected from CHD patients for study analysis, and the Gensini score was recorded for the assessment of coronary artery stenosis degree. Peripheral blood samples of all subjects were collected after enrollment. Then, serum samples were isolated by density gradient centrifugation, which were used to detect brain-derived neurotrophic factor (BDNF) level by enzyme-linked immunosorbent assay (ELISA) using Total BDNF Quantikine ELISA Kit (Cat. No. DBNT00, sensitivity 1.35 pg/mL). Besides, the serum samples of CHD patients were used to examine the level of tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, IL-6, IL-8, IL-17A, vascular cell adhesion molecule-1 (VCAM-1), and intercellular adhesion molecule-1 (ICAM-1). The kits used for the detection of inflammatory cytokines and adhesion molecules were as follows: Human TNF-α Quantikine ELISA Kit (Cat. No. DTA00D, sensitivity 6.23 pg/mL), Human IL-1β/IL-1F2 Quantikine ELISA Kit (Cat. No. DLB50, sensitivity 1 pg/mL), Human IL-6 Quantikine ELISA Kit (Cat. No. D6050, sensitivity 0.7 pg/mL), Human IL-8/CXCL8 Quantikine ELISA Kit (Cat. No. D8000C, sensitivity 7.5 pg/mL), Human IL-17 Quantikine ELISA Kit (Cat. No. D1700, sensitivity 15 pg/mL), Human VCAM-1/CD106 Quantikine ELISA Kit (Cat. No. DVC00, sensitivity 1.26 ng/mL), and Human ICAM-1/CD54 Quantikine ELISA Kit (Cat. No. DCD540, sensitivity 0.254 ng/mL). All kits used in the study were purchased from R&D Systems, China. The experiments were performed based on the manufacturer’s instructions.

2.3 | Statistics

Statistical analyses were carried out using SPSS 24.0 (IBM Corp.,). Graphs were constructed using GraphPad Prism 6.01 (GraphPad Software Inc.). The level of BDNF among three groups was compared using the Kruskal–Wallis H rank-sum test, and post hoc comparisons were analyzed using the Bonferroni test. The performances of BDNF levels in distinguishing different subjects were evaluated using receiver operating characteristic (ROC) curves. The BDNF level in patients with different clinical characteristics was compared using the Mann–Whitney U test. Correlations between BDNF level and clinical data were checked using the Spearman correlation test. p < 0.05 was considered significant.

3 | RESULTS

3.1 | Clinical characteristics

Among the 207 enrolled CHD patients, their age was 62.5 ± 10.2 years, which consisted of 47 (22.7%) women and 160 (77.3%) men, among which 150 (72.5%), 117 (56.5%), and 54 (26.1%) patients were complicated with hypertension, hyperlipidemia, and diabetes mellitus (DM), respectively. Fifty-two (25.1%) patients had a family history of coronary artery disease (CAD). Their median (interquartile range [IQR]), triglyceride (TG), total cholesterol (TC), and low-density
lipoprotein cholesterol (LDL-C) values were 1.8 (1.0–2.5) mmol/L, 4.6 (3.8–5.3) mmol/L, and 3.2 (2.6–3.9) mmol/L, respectively. Apart from that, the median (IQR) Gensini score was 34.0 (18.0–57.0). Other detailed information is listed in Table 1.

3.2 | BDNF level

BDNF was varied among CHD patients, DCs, and HCs (p < 0.001; Figure 1A). In detail, it was lowest in CHD patients (median [IQR]: 5.6 (3.5–9.6) ng/mL), followed by DCs (median [IQR]: 10.7 (6.1–17.0) ng/mL), and highest in HCs (median [IQR]: 12.6 (9.4–18.2) ng/mL). The post hoc comparison revealed that BDNF was lower in CHD patients than in DCs and HCs (both p < 0.001). Furthermore, BDNF could well distinguish CHD patients from DCs (area under the curve [AUC]: 0.857) (Figure 1B).

3.3 | Association between BDNF and clinical characteristics and stenosis

BDNF was negatively linked with TG (r_s = -0.170, p = 0.014), TC (r_s = -0.145, p = 0.037), and LDL-C (r_s = -0.183, p = 0.008); meanwhile, decreased BDNF was associated with the occurrence of DM (p = 0.001) in CHD patients (Table 2). The Gensini score was applied to assess the stenosis, and it was shown that BDNF was negatively correlated with the Gensini score in CHD patients (r_s = -0.285, p < 0.001; Figure 2). BDNF was not correlated with other CHD patients’ characteristics. Furthermore, the correlation of BDNF with stenosis in elder (>60 years) and younger (≤60 years) patients was determined, which showed that BDNF was negatively correlated with stenosis both in elder patients (r_s = -0.288, p = 0.002; Figure S1A) and in younger patients (r_s = -0.322, p = 0.002; Figure S1B).

3.4 | Association between BDNF and inflammation and adhesion molecules

BDNF was negatively linked with CRP (r_s = -0.261, p < 0.001) and some of the pro-inflammatory cytokines, including TNF-α (r_s = -0.271, p < 0.001), IL-1β (r_s = -0.183, p = 0.008), and IL-8 (r_s = -0.322, p < 0.001); however, BDNF was not correlated with IL-6 (r_s = -0.110, p = 0.115) or IL-17A (r_s = -0.098, p = 0.159) in CHD patients (Figure 3A–F). In terms of the adhesion molecules, BDNF was negatively related to VCAM-1 (r_s = -0.240, p < 0.001; Figure 4A) and ICAM-1 in CHD patients (r_s = -0.205, p = 0.003; Figure 4B).

4 | DISCUSSION

Some findings were non-neglectable in this study: BDNF was decreased in CHD patients compared with DCs and HCs; BDNF was negatively related to TG, TC, and LDL-C in CHD patients; BDNF was negatively associated with CRP, TNF-α, IL-1β, IL-8, VCAM-1, and ICAM-1 in CHD patients; and BDNF was negatively linked with the stenosis degree of CHD patients. Furthermore, BDNF could well distinguish CHD patients from DCs and HCs. The possible explanation could be that BDNF plays a cardiovascular-protective role in CHD through association with inflammation and adhesion molecules.
enhancing lipid metabolism, against atherosclerosis, and reducing the inflammatory response, while these biological processes (lipid metabolism, atherosclerosis, and inflammatory response) are aggravated in CHD patients, which means that the physiological effect of BDNF is restrained, indicating its decreased expression. Therefore, the BDNF is decreased in CHD patients compared with DCs and HCs.

Dysregulation of lipid metabolism is a major aspect involved in the pathogenesis and progression of CHD. Even though BDNF could regulate lipid metabolism at the molecular level, there are still few studies that report its relationship with the lipid in CHD patients. In this study, it is disclosed that BDNF was negatively correlated with TG, TC, and LDL-C in CHD patients, which could be explained as follows: BDNF participates in the biosynthesis of apoE, which is closely related to the metabolism of TG, TC, and LDL-C; therefore, intercorrelation is observed between BDNF and these lipids; BDNF is reported to promote the efflux of intracellular cholesterol; therefore, BDNF is associated with TG, TC, and LDL-C in CHD patients.

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The adhesive molecules have also been reported to play an important role in the pathogenesis of CHD patients; for instance, one study discloses that the intercellular adhesion molecule-1 (ICAM1) polymorphism is involved in the occurrence of CHD. The correlation of BDNF with inflammation has been reported in several studies. For instance, one study shows that the BDNF is associated with IL-6 in diabetes mellitus patients. Another study

Table 2: Correlation of BDNF with clinical characteristics in CHD patients

| Items          | BDNF (ng/mL), median (IQR) | \(r/Z/\chi^2\) value | \(p\) value |
|----------------|-----------------------------|-----------------------|-------------|
| Age (years)    | -                           | -0.081                | 0.248       |
| BMI (kg/m²)    | -                           | 0.030                 | 0.671       |
| FBG (mmol/L)   | -                           | 0.035                 | 0.614       |
| Scr (μmol/L)   | -                           | -0.109                | 0.118       |
| SUA (μmol/L)   | -                           | -0.008                | 0.905       |
| TG (mmol/L)    | -                           | -0.170                | 0.014       |
| TC (mmol/L)    | -                           | -0.145                | 0.037       |
| LDL-C (mmol/L) | -                           | -0.183                | 0.008       |
| HDL-C (mmol/L) | -                           | 0.074                 | 0.292       |
| Gender         |                             | -0.611                | 0.541       |
| Female         | 4.6 (3.3–8.7)               |                       |             |
| Male           | 5.7 (3.5–9.6)               |                       |             |
| Smoke          |                             | 0.606                 | 0.739       |
| Never          | 5.9 (3.5–10.1)              |                       |             |
| Former         | 5.2 (3.6–8.9)               |                       |             |
| Current        | 5.6 (3.6–8.9)               |                       |             |
| Hypertension   |                             | -0.761                | 0.447       |
| No             | 6.2 (3.5–11.5)              |                       |             |
| Yes            | 5.4 (3.6–9.0)               |                       |             |
| Hyperlipidemia |                             | -0.114                | 0.910       |
| No             | 5.7 (3.6–9.1)               |                       |             |
| Yes            | 5.4 (3.5–9.6)               |                       |             |
| DM             |                             | -3.202                | 0.001       |
| No             | 6.1 (3.8–9.9)               |                       |             |
| Yes            | 4.0 (3.2–8.6)               |                       |             |
| Family history of CAD |                   | -0.819                | 0.413       |
| No             | 5.5 (3.5–9.1)               |                       |             |
| Yes            | 5.9 (3.5–10.4)              |                       |             |

Abbreviations: BDNF, brain-derived neurotrophic factor; BMI, body mass index; CAD, coronary artery disease; DM, diabetes mellitus; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; Scr, serum creatinine; SUA, serum uric acid; TC, total cholesterol; TG, triglyceride.
discloses that BDNF could reduce the inflammation in experimental Streptococcus pneumoniae meningitis. In our study, we found that BDNF was negatively associated with the inflammation and adhesion molecules in CHD patients. These findings could be explained as that: (1) the upregulation of BDNF might decrease TNF-α and IL-1β; therefore, the BDNF is negatively associated with TNF-α and IL-1β; (2) BDNF might be involved in regulating the expression of the pro-inflammatory cytokines via modulating the TLR4/NF-κB p65 signaling; therefore, BDNF is negatively associated with the pro-inflammatory cytokines (including TNF-α and IL-1β); (3) BDNF could inhibit the ICAM-1 expression in IL-1β-treated endothelial cells; hence, the BDNF was negatively related to ICAM-1 in CHD patients; (4) VCAM-1 has been implicated in the development of a variety of pathophysiological states in the brain and in the body periphery; meanwhile, the BDNF is also reported to be involved in these biological processes; therefore, the intercorrelation between them was observed in this study.

Regarding the association between BDNF and stenosis in CHD patients, only one study reports that BDNF is positively correlated with the number of stenosis vessels, while no study evaluates the relationship between BDNF and the stenosis degree in CHD patients. In this study, we found that BDNF was negatively associated with the Gensini score in CHD patients. This phenomenon could be explained as that: (1) BDNF could regulate the metabolism of lipids and promote the efflux of intracellular cholesterol, which are closely related to the exacerbation of stenosis in CHD patients; therefore,
BDNF is negatively associated with the Gensini score in CHD patients; (2) BDNF could help to confer protection against atherosclerosis as mentioned above, and the formation of atherosclerotic plaque would directly accentuate the stenosis in CHD patients; therefore, the BDNF is negatively associated with the Gensini score in CHD patients.15

Even though a lot of biomarkers have been discovered for indicating the prognosis of CHD, it still needs more study to detect the potential biomarkers with higher utility in indicating the prognosis of CHD patients to better realize the risk stratification and individualized treatment. The present study existed some limitations: (1) The sample size was relatively small, which might cause the low statistical power; (2) the detailed mechanism of BDNF in regulating the progression of CHD patients still needed further in vitro and in vivo studies; (3) multiple time points determining BDNF expression in the natural disease course of CHD patients were needed to verify BDNF’s effect on monitoring the progression and prognosis of CHD patients; (4) the correlation of BDNF with the atherosclerotic plaque formation could be detected in the further study; (5) the association between BDNF and the survival of CHD patients could be detected in further study; (6) only the Gensini score was not enough in indicating the stenosis of CHD patients; further study could also detect the fractional flow reserve for further reflecting the stenosis of CHD patients; (7) as the time from the end of the study to now was short, the follow-up data were not presented, which would be shown in the further study.

In conclusion, BDNF reflects the lipid dysregulation, inflammatory status, and stenosis degree in CHD patients.

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None.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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**SUPPORTING INFORMATION**

Additional supporting information may be found in the online version of the article at the publisher’s website.

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