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Journal of Diabetes and Its Complications xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

Brain-derived neurotrophic factor correlated with muscle strength in subjects undergoing stationary bicycle exercise training

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ARTICLE INFO

Article history:
Received 26 November 2014
Received in revised form 27 January 2015
Accepted 31 January 2015
Available online xxxx

Keywords:
Brain-derived neurotrophic factor
Body weight
Bicycle exercise
Metabolic syndrome
Muscle strength

ABSTRACT

Aims: Several central nervous disorders are associated with metabolic syndrome (MetS) and type 2 diabetes. Reduction in brain-derived neurotrophic factor (BDNF) is involved in the mechanism of central nervous dysfunction. BDNF is up-regulated after exercise, but it is not known whether increased BDNF is related to increases in muscle strength.

Methods: In the present study, subjects with MetS or type 2 diabetes were enrolled in an exercise program. All participants underwent an indoor bicycle exercise program for twelve weeks. Serum BDNF was determined after overnight fasting. Muscle strength was assessed by extension of the dominant lower extremity.

Results: A total of 33 subjects were enrolled in this study. The body mass index did not change significantly (from 30.4 ± 6.0 to 30.2 ± 5.8 kg/m^2, $P = 0.436$), but serum BDNF increased significantly (from 17.1 ± 9.1 to 24.2 ± 10.7 ng/mL, $P < 0.001$) after the study. The exercise-associated BDNF was significantly correlated with the increased strength in lower-extremity extension test ($r = 0.54$, $P = 0.001$). Using multivariate regression analysis, muscle-strength increment, but not body-weight change, was an independent factor for serum BDNF (95% CI = 0.009–0.044, $P = 0.005$).

Conclusions: After a twelve-week program of stationary bicycle exercise, serum BDNF concentration increased, and this change was positively correlated with muscle strength of lower-extremity extension, but not body weight. (**Trial registration**: NCT02268292, ClinicalTrials.gov)

1. Introduction

Metabolic syndrome (MetS), with a cluster of cardiovascular risks, has become an important public health problem worldwide (Beltran-Sanchez, Harhay, Harhay, & McElligott, 2013; Liu et al., 2013; Yeh, Chang, & Pan, 2011; Zimmet, Magliano, Matsuzawa, Alberti, & Shaw, 2005). In addition to an increased risk of cardiovascular disease (Mottillo et al., 2010; Sattar et al., 2003), MetS is also associated with central nervous disorders. It has been reported that MetS is prevalent in subjects with depression or schizophrenia (Pan et al., 2012; Papanastasiou, 2013; Suttajit & Pilakanta, 2013). Similarly, a high prevalence of depression is also observed in subjects with type 2 diabetes (Mezuk et al., 2013).

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophins involved in developing neurons and regulating synaptic activities (Lebrun, Bariohay, Moyse, & Jean, 2006; Lewin & Barde, 1996). Severities in depression, as well as schizophrenia, were associated with low serum BDNF concentration, which is correlated with its concentration in the central nervous system (Jindal et al., 2010; Molendijk et al., 2013; Pan, Banks, Fasold, Bluth, & Kastin, 1998; Rizos et al., 2008). Furthermore, BDNF also has an effect on maintaining energy homeostasis (Nakagawa et al., 2000; Toriya et al., 2010). It was reported that low serum BDNF concentrations were observed in subjects with insulin resistance, MetS or type 2 diabetes (Karczewska-Kupczewska et al., 2011; Krabbe et al., 2009; Levinger et al., 2008).

Conflict of Interest: The authors declare that they have no competing interests.

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http://dx.doi.org/10.1016/j.jdiacomp.2015.01.014
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BDNF can increase following a life-style intervention combined with caloric restriction and exercise training (Kishi & Sunagawa, 2012; Lee et al., 2014). However, the up-regulation of BDNF after exercise is not associated with a body weight change (Cho et al., 2012; Kishi & Sunagawa, 2012; Zoladz et al., 2008). Furthermore, it was recently reported that serum BDNF was not associated with visceral fat measured using magnetic resonance imaging (Lee et al., 2012). It has been shown that BDNF is expressed after exercise in skeletal muscle as an endocrine organ in an in vitro study (Matthews et al., 2009). To understand the effects of skeletal muscle on BDNF during exercise (Pedersen et al., 2009), we conducted a prospective study to assess the relationship between muscle strength and BDNF in an exercise program.

2. Subjects and methods

2.1. Study subjects

This prospective open-labeled study was conducted at Taichung Veterans General Hospital. Adult participants with metabolic syndrome and/or type 2 diabetes were enrolled. Exclusion criteria were (1) hyperglycemic crisis or HbA1c > 12%; (2) acute or chronic renal diseases with serum creatinine levels greater than 200 mmol/L; (3) acute or chronic infectious diseases; (4) changes in medications for diabetes, hypertension, hyperlipidemia, anti-platelet or anti-inflammation in the past month; or (5) limitations in the ability to undertake regular exercise, based on clinical judgment. Anthropometric measurements were performed in the morning after an over-night fasting period. Blood pressure was detected after subjects had sat and rested for 10 min. MetS is defined as the presence of three or more of the following components based on the modified Third Report of the National Cholesterol Education Program (NCEP) criteria: (1) waist circumference > 90 cm in men or > 80 cm in women, (2) triglycerides > 150 mg/dl (1.7 mmol/L), (3) high-density lipoprotein (HDL) cholesterol < 40 mg/dl (1.0 mmol/L) in men or < 50 mg/dl (1.3 mmol/L) in women, (4) blood pressure > 130/85 mmHg or using antihypertensive medications and (5) fasting glucose > 100 mg/dl (5.6 mmol/L) or using antidiabetic medications (Grundy et al., 2005). The diagnosis of diabetes in the current study was based on the American Diabetes Association (2012)) criteria. This study complies with the Declaration of Helsinki, and the research protocol was approved by the Institutional Review Board of Taichung Veterans General Hospital. Written informed consent was provided by all participants.

2.2. Exercise testing protocol and determination of exercise intensity

The procedures were fully explained to all subjects before the cardiopulmonary exercise test. The subjects exercised using a Master-Screen CPX (CareFusion Respiratory Care, CA, USA) with a cycle ergometer. After a three-minute rest period, the subjects initially cycled for 3 min at 10 W for the baseline warm-up. Subsequently, the exercise load increased at increments of 10 W/min. The pedal rate was set at 60 rotations per minute (rpm) during the whole test (Wu, Lin, Chen, & Tsai, 2006). The subjects were encouraged to continue exercising until exhaustion or the following criteria were achieved: (1) rating of perceived exertion (RPE) > 17, (2) respiratory exchange ratio (RER) > 1.10, (3) plateau in oxygen uptake (VO_2) despite increasing workload, and (4) heart rate > 85% of the age-predicted maximal rate. The ventilatory threshold (VT) was determined by the V-slope method.

2.3. Stationary bicycle exercise

All enrolled subjects received a scheduled twelve-week exercise program. A commercially available bicycle (Giant CS800, Taichung, Taiwan) with an indoor bicycle stand (Giant Cyclotron Mag, Taichung, Taiwan) was used as the home exercise training modality. The mean VO_2 that correlated with VT was used as the target of training intensity at home. Initially, a 5-min warm-up period at an intensity of RPE 9 was suggested. Subsequently, bicycle exercise at the recommended training intensity was started and maintained for 40 min, followed by a 5-min cool down period. Instruction for indoor use of the bicycle was given by the same senior physical therapist. During the study period, diet control was maintained. No medications were changed during the study.

2.4. Isokinetic test

A Biodex Isokinetic Dynamometer (Biodex Medical Systems, Inc., Shirley, New York, USA) was used to evaluate the quadricep strength of the subjects. Before each testing session, the dynamometer was gravitationally corrected in accordance with the manufacturer's recommendations. Each subject was seated with their thighs at an angle of 85° to the trunk and was secured with snug straps. The mechanical axis of the dynamometer was aligned with the lateral epicondyle of the knee. The muscle strength was assessed by the extension of the dominant lower extremity for 6 repetitions at maximal effort.

2.5. Biochemical measurements

Blood samples were collected for the measurement of glucose, insulin, glycosylated hemoglobin (HbA1c), lipoprotein profiles, liver enzymes, creatinine, C-reactive protein (CRP), myostatin, follistatin, and BDNF at fasting and rest status before and after the exercise-training program. Glucose, creatinine, liver enzymes, triglyceride and cholesterol concentrations were measured using commercial kits (Beckman Coulter, Fullerton, U.S.A). Insulin, HDL cholesterol and low-density lipoprotein (LDL) cholesterol levels were also measured using commercial kits (Roche Diagnostics GmbH, Mannheim, Germany). CRP was measured by the immunochemical assay of purified Duck IgY (ΔFc) antibodies (Good Biotech Corp., Taichung, Taiwan). Myostatin was measured using an enzyme immunoassay (R&D Systems, Minneapolis, USA); the intra-assay and inter-assay CVs were 1.8% and 3.1%, respectively, with a sensitivity of 0.003 ng/mL. Myostatin was measured using an enzyme immunoassay (R&D Systems, Minneapolis, USA); the intra-assay and inter-assay CVs were 3.7% and 9.2%, respectively, with a sensitivity of 0.03 ng/mL. Human BDNF was measured using an enzyme immunoassay (R&D Systems, Minneapolis, USA); the intra-assay and inter-assay CVs were 4.1% and 9.0%, respectively, with a sensitivity of 0.02 ng/mL. Homeostasis model assessment insulin resistance (HOMA IR) index = [fasting insulin (μIU/mL) * fasting glucose (mmol/L)]/22.5.

2.6. Statistical analysis

All of the descriptive data were presented as the mean ± standard deviation (SD). Statistical analyses were conducted by a paired t-test to compare differences before and after intervention. Because of the skewed distribution, data for CRP triglycerides, HOMA-IR and insulin were logarithm-transformed (log) in the analyses. The correlations of BDNF with other variables were determined by Pearson's correlation. Multivariate linear regression analysis was used to analyze the associated factors of change in BDNF. Statistical analysis was performed by SPSS 19.0 (IBM, Armonk, NY, USA).

3. Results

Of the 40 subjects assessed for eligibility, 33 subjects satisfied the criteria and all of them completed the assessment after completion of the exercise program. The mean age was 52.1 ± 10.9 years, and thirty (90.9%) of them were type 2 diabetic patients (Table 1). The dominant lower extremity was the right side in all of the study subjects. The mean VO_2 correlated with VT was 63.6% ± 8.5% of VO_{2max} after exercise-testing assessment, and 65%VO_{2max} was used as the training intensity for bicycle exercise.

Please cite this article as: Tsai, S-W., et al., Brain-derived neurotrophic factor correlated with muscle strength in subjects undergoing stationary bicycle exercise training, *Journal of Diabetes and Its Complications* (2015), http://dx.doi.org/10.1016/j.jdiacomp.2015.01.014