

## Brain-derived neurotrophic factor in blood increases transiently after single sessions of moderate intensity exercise in obese females

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### Abstract

This study aimed to analyze the increase in serum BDNF levels after moderate-intensity exercise in obese females. This study used the True-Experimental method with the Randomized Control Group Pre-test-Post-test design. A total of 14 obese female adolescents aged 19-24 years participated in this study and were divided into two groups, i.e., the control group (CG, n=7) and the moderate-intensity exercise group (MIEG, n=7). The exercise was performed with an intensity of 64 – 76 HRmax for 40 minutes using a Richter Treadmill (4.0 HP DC). Moderate-intensity exercise was carried out in one intervention. Blood sampling was carried out before and after moderate-intensity exercise on the cubital vein as much as 3 ml. Examination of serum BDNF levels using the ELISA method. The data analysis technique used the Independent Samples T-Test test with SPSS version 21. The results of statistical analysis show that the mean pre-test serum BDNF levels were CG (258.66±27.11 pg/mL), MIEG (252.48±23.17 pg/mL), and (p=0.865). The mean post-test serum BDNF levels were CG (236.22±20.83 pg/mL), MIEG (497.73±59.55 pg/mL), and (p=0.001). The mean delta of serum BDNF levels on CG (-22.43±26.04), MIEG (245.25±61.57 pg/mL), and (p=0.002). Based on the study results, it is concluded that a single session of moderate-intensity exercise in the morning increases serum BDNF levels in obese females. It is recommended for future research comparing acute vs. chronic exercise to increase serum BDNF levels.

**Keywords:** BDNF, moderate-intensity exercise, obesity, cognitive function

### INTRODUCTION

To date, obesity remains a health problem for countries worldwide (de Oliveira *et al.*, 2019). It is because the obesity prevalence in the worldwide population aged ≥ 18 years continued to increase from 1975 by (4.7%) to 2016 by (13%), with the highest prevalence increase in females (15%), followed by males (11%) (WHO, 2016). It is estimated that in 2025, such a prevalence will continue to rise to 18% for males and 21% for females (NCD-RisC, 2016). The obesity prevalence increase also occurs in several

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Indonesian populations. Based on the Basic Health Research (RISKESDAS) of 2018, the obesity prevalence in Indonesia aged  $\geq 18$  years increased from 10.5% in 2017 to 21.8% in 2018 (Risikesdas, 2018). This obesity prevalence increase can become a serious problem since it affects mortality and morbidity (Busutil *et al.*, 2017). However, problems associated with obesity still have no specific considerations.

Obesity is a global health problem to be considered since it increases the risk of various chronic diseases, e.g., type 2 diabetes (T2D), hypertension, and cardiovascular disease (CVD) (Gadde *et al.*, 2018). Also, obesity is linked to the risk of cognitive functional degradation (Cook *et al.*, 2017). Cognitive functional degradation in obesity is associated with neuro injuries (Pugazhenthii *et al.*, 2017), causing changes in the brain structure (Wang *et al.*, 2016) as volume decrease in the brain region contributing to managing cognitive functions; one of which is the hippocampus (Perosa *et al.*, 2020). Cognitive functional degradation in obesity has a positive correlation with the declining level of brain-derived neurotrophic factor (BDNF) (Rodriguez *et al.*, 2018; Atake *et al.*, 2018). BDNF has a vital role in neuroprotection through a mechanism (neurogenesis, cellular survival, axonal growth, dendritic growth, and synaptic plasticity) activated via the link between BDNF and Tropomyosin receptor kinase B (TrkB) (Konishi *et al.*, 2020). Therefore, a specific strategy is required to increase the BDNF level in preventing cognitive functional degradation in obesity. One strategy is a non-pharmacological approach based on physical exercises (Alomari *et al.*, 2020; Jiménez-Maldonado *et al.*, 2018).

Physical exercises are one of the non-pharmacological mechanisms in improving cognitive functions with the BDNF level increase parameter (Marquez *et al.*, 2015). Physical exercises can induce the *D*- $\beta$ -hydroxybutyrate (DBHB) synthesis in the liver, circulated to the brain and peripheral organs. DBHB induces BDNF expression by inhibiting *histone deacetylase 2* (HDAC 2) and HDAC 3 at the hippocampus (Pranoto *et al.*, 2020; Sleiman *et al.*, 2016). The National Heart, Lung, and Blood Institute (NHLBI) also recommends that moderate-intensity exercises may be used

as an excellent therapy in managing obesity-based complications (Karri et al., 2019). A precedent study reported that moderate-intensity acute exercises using a treadmill on non-obese humans increased the BDNF serum level (Tsai et al., 2016). Moderate-intensity acute exercises were also proven to increase the BDNF level in obese subjects (Inoue et al., 2020; Dinoff et al., 2016; Szuhany et al., 2015). Another predecessor study reported that acute exercises significantly increased the BDNF serum level (Briken et al., 2016). However, several previous study results also reported that moderate-intensity exercises did not significantly increase the BDNF level between pre and post-exercise (Antunes et al., 2020). Another previous study also reported that aerobic exercise with a 65–85% HR<sub>max</sub> intensity did not cause a significant change in BDNF level in obese adolescents (Goldfield et al., 2018). Therefore, the effective and efficient physical exercise dosage to increase BDNF level in preventing cognitive functional degradation in obesity remains unexploited clearly.

Given this background, this study aimed to analyze the BDNF serum level increase after moderate-intensity exercises on obese females. Based on this objective, the researchers hypothesized that the BDNF serum level increases after moderate-intensity acute exercises (60-70% HR<sub>max</sub>) on obese females.

## **METHOD**

### **Study design**

The study was True-Experimental with the Randomized Control Group Pre-test-Post-test design. Fourteen obese female adolescents participated in this study. The inclusion criteria are aged 19-24 years, with a body mass index (BMI) of 27-32 kg/m<sup>2</sup>, normal blood pressure, normal rest pulse, oxygen saturation (SpO<sub>2</sub>) of 95-100%, and fasting blood glucose (FBG) under 100 mg/dL. Subjects were randomly classified into the control group (CG, n = 7) and the moderate-intensity exercise group (MIEG, n = 7). Subjects were collected using the consecutive sampling technique. It is a subject selection technique by determining subjects based on study criteria in a particular period to complete the required subject amount (Nursalam, 2003). All

subjects were informed verbally and in writing regarding the study. Subjects filled out and signed informed consent before participating in the study. The Health Research Ethic Committee had approved all study procedures of the Faculty of Medicine Universitas Brawijaya Malang number 81/EC/KEPK–S1/04/2020.

### **Exercise protocol**

The physical exercise was performed with a 60-70% HR<sub>max</sub> intensity for 40 minutes, with details of a 5-minute warming up (50-60% HR<sub>max</sub>), 30-minute continuous movements (60-70% HR<sub>max</sub>), and 5-minute cooling down (50-60% HR<sub>max</sub>) (Rejeki *et al.*, 2021). The physical exercise was executed from 07.00-09.00 WIB (Nygaard *et al.*, 2015; Kraemer *et al.*, 2014) using a Richter Treadmill (4.0 HP DC). During the moderate-intensity physical exercise, the heart rate monitoring employed the Polar Heart Rate Monitor (Polar H10 Heart Rate Sensor, Inc., USA). During the physical exercise period, all subjects in the control group remained sitting and resting until the exercise was completed.

### **Measurement of body composition and physiological factors**

Height measurement used the Stadiometer (Portable Seca® Stadiometer, North America). Weight measurement utilized a digital balance (OMRON Model HN-289, Omron Co., Osaka, Japan). The body mass index (BMI) was measured by calculating weight (kg) divided by height (m). The blood pressure was measured using an OMRON digital sphygmomanometer (OMRON Model HEM-7130 L, Omron Co., Osaka, Japan) on the non-dominant arm three consecutive times within a 1-2-minute interval between two measurements. The subject was seated during blood pressure measurement. Resting heart rate and SpO<sub>2</sub> were measured using the Beurer Pulse Oximeter (PO 30 Pulse Oximeter). FBG examination was performed using Accu-Chek Performa (Roche, Mannheim, Germany) with an mg/dL unit.

### **Blood sample collection and examination**

Blood was collected on the vena cubiti for 3ml. During the blood collection, the subject was in a laying position. Blood collection was performed twice, i.e., 30 minutes pre-exercise and 10 minutes post-exercise. Blood was centrifuged for 15 minutes at 3000 rpm. Serum was separated and stored at -80°C for BDNF level analysis on the following day. BDNF serum level was evaluated at the Physiology Laboratory of Faculty of Medicine Universitas Brawijaya Malang using the Enzyme-Linked Immunosorbent Assay (ELISA) kit (Catalog No. E-EL-H0010; Elabscience, Inc., China) with a standard curve range of 31.25-2000 pg/mL and the irisin sensitivity level in the kit was 18.75 pg/mL.

### **Statistical analysis**

The statistical analysis was carried out using Statistic Package for Social Science (SPSS) version 21 (Chicago, IL, USA). The normality test employed Shapiro-Wilk, while the difference test used Paired Sample T-Test and Independent Samples T-Test. All data are presented with mean  $\pm$  Standard Error of Mean (SEM). All statistical analyses utilized a significance level ( $P < 0.05$ ).

## **RESULTS**

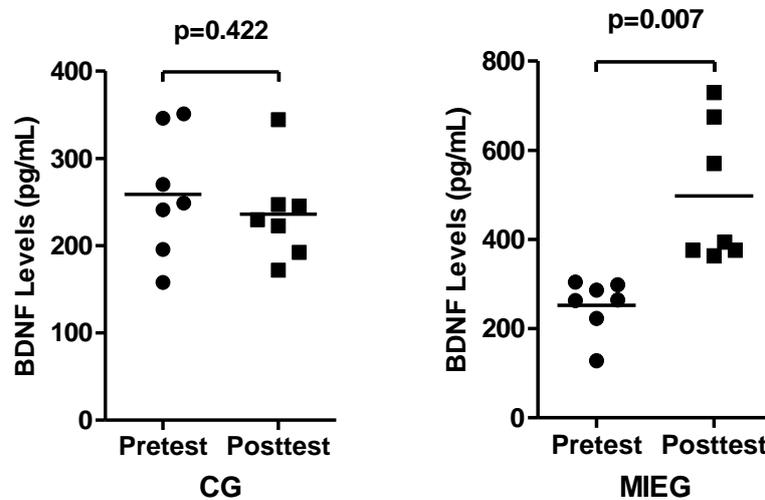
The statistical analysis results of study subject characteristics, including age, height, weight, BMI, SBP, DBP, RHR, SpO<sub>2</sub>, and FBG, on each group are presented in Table 1.

**Table 1.** Statistical Analysis Results of Study Subject Characteristics

Parameter	Group				P-value
	CG (n=7)		MIEG (n=7)		
	Mean	SEM	Mean	SEM	
Age (years)	21.43	0.65	21.57	0.64	0.879
Height (m)	1.60	0.02	1.58	0.02	0.530
Weight (kg)	74.83	2.47	73.99	2.94	0.830
BMI (kg/m <sup>2</sup> )	29.67	0.64	29.26	0.43	0.601
SBP (mmHg)	115.43	1.09	114.14	1.10	0.422
DBP (mmHg)	75.57	1.07	74.43	1.41	0.530
RHR (bpm)	70.71	3.19	72.29	1.48	0.663
SpO <sub>2</sub> (%)	97.86	0.59	97.29	0.52	0.484
FBG (mg/dL)	92.71	1.89	88.14	2.46	0.166

Note: BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; RHR: Resting heart rate; SpO<sub>2</sub>: Oxygen saturation; FBG: Fasting blood glucose. CG: Control group; MIEG: Moderate-intensity exercise group. p-Value was acquired using the Independent Samples T-Test to compare subject characteristics between CG and MIEG. All data present mean±SEM.

Table 1 of the Independent Samples T-Test results shows an insignificant difference between all study subject characteristics in each group (P>0.05). The BDNF serum level difference test results between pre-test and post-test on CG and MIEG are presented in Figure 1.



**Figure 1.** Average BDNF serum level on each group

Note: CG: Control group; MIEG: Moderate-intensity exercise group. p-Value was acquired using the Paired Sample T-Test. All data present mean±SEM.

Figure 1 shows that the average post-test BDNF serum level is higher than the pre-test on each group. Based on the Paired Sample T-Test, there was no significant difference of average BDNF serum level between pre-test and post-test on CG (P>0.05), while the BDNF serum level between

pre-test and post-test on MIEG showed a significant difference ( $P < 0.05$ ). The analysis results of average BDNF serum level between pre-test (CG\*MIEG), post-test (CG\*MIEG), and delta (CG\*MIEG) are presented in Figure 2.

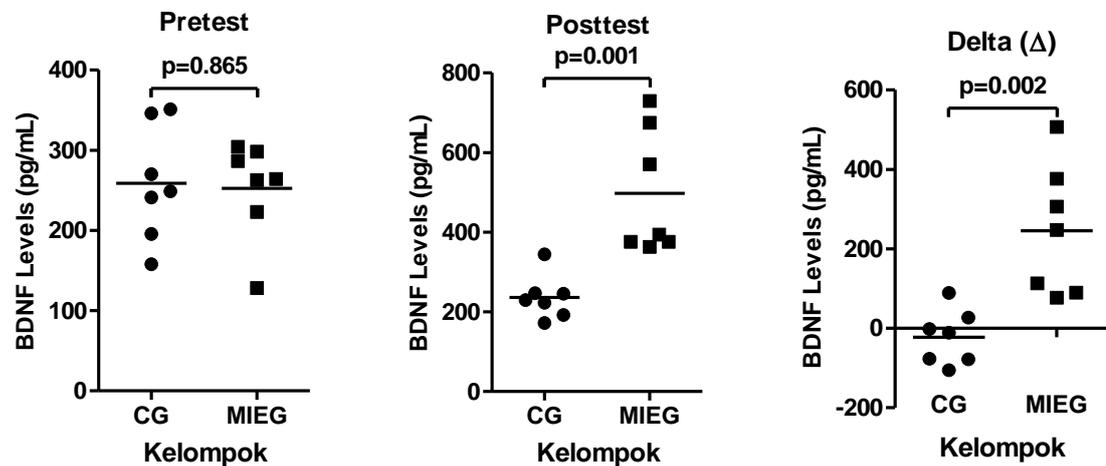


Figure 2. BDNF serum level in pre-test (CG\*MIEG), post-test (CG\*MIEG), and delta (CG\*MIEG)

Note: CG: Control group; MIEG: Moderate-intensity exercise group. p-Value was acquired using the Independent Samples T-Test. All data present mean $\pm$ SEM.

Figure 2 reveals that the average pre-test BDNF serum level was similar in both groups, while the average post-test BDNF serum level on MIEG was higher than CG. The Independent Samples T-Test results show an insignificant difference of average pre-test BDNF serum level between CG and MIEG ( $P > 0.05$ ), while the average post-test and delta BDNF serum level between MIEG and CG had a significant difference ( $P < 0.05$ ).

## DISCUSSION

Based on the Independent Samples T-Test analysis results, subject characteristics including age, height, weight, BMI, SBP, DBP, RHR, SpO<sub>2</sub>, and FBG show an insignificant difference in all groups (Table 1). This finding follows a precedent study reporting an insignificant difference of study subject characteristics, including age, height, weight, BMI, waist circumference (WC), and body fat percentage on each group (Domínguez-Sánchez et al., 2018). Another study also reported no significant differences in study subject characteristics, including age, height, weight, BMI, WC, and body fat percentage (Alomari et al., 2020). Therefore, based on the study

subject characteristics analysis results, both groups were on the same starting point before the moderate-intensity exercise intervention. Hence, any changes in the BDNF serum level do not come from the subject characteristics but due to the physical exercise intervention.

The Paired Sample T-Test results show an insignificant increase of average BDNF serum level between pre-test and post-test on the control group (CG), while the BDNF serum level between pre-test and post-test on the moderate-intensity exercise group (MIEG) showed a significant increase (Figure 1). It is in line with a predecessor study, concluding a significant increase of mature BDNF (mBDNF) concentration between pre-exercise and post-exercise moderate-intensity continuous training (MICT) on obese males (Inoue et al., 2020). Another study also reported that moderate-intensity acute exercise also significantly increased the BDNF serum level (Briken et al., 2016). The physical exercise intervention effect can cause increased BDNF serum level on MIEG. Physical exercise can stimulate D- $\beta$ -hydroxybutyrate (DBHB) synthesis in the liver, followed by circulation to the hippocampus and peripheral organs (Pranoto et al., 2020; Sleiman et al., 2016). In the hippocampus, DBHB induces increased BDNF expression by inhibiting histone deacetylases 2 (HDAC 2) and histone deacetylases 3 (HDAC 3) (Wang & Holsinger, 2018). Increased BDNF expression will bind the tropomyosin-receptor-kinase B (TrkB) receptor, where the link of BDNF and TrkB promotes survival of cells (Bathina & Das, 2015), increases neurogenesis and synaptogenesis in the hippocampus (Mustrop et al., 2015), increases neuron proliferation and differentiation (Lee et al., 2016), and decreases hippocampus neuron apoptosis (van Praag et al., 2005) by signaling p38-mitogen-activated protein kinase (p38-MAPK) dependent (Widyanto & Hermanto, 2013). This mechanism indirectly contributes to increasing cognitive functions (Marquez et al., 2015).

The study results show that the post-test BDNF serum level on MIEG was higher than CG (Figure 2). The Independent Samples T-Test analysis results reveal a significant difference in average post-test BDNF serum level between MIEG and CG. Also, delta ( $\Delta$ ) post-test – pre-test between MIEG

and CG show a significant difference (Figure 2). It follows a meta-analysis by [Dinoff et al. \(2016\)](#), reporting that one exercise session (acute exercise) increased BDNF concentration in the peripheral circulation. [Cho et al. \(2012\)](#) also discovered that acute exercise significantly increased BDNF concentration stored in platelets. A study by [Rasmussen et al. \(2009\)](#) reported increased BDNF serum concentration post-acute exercise. Increased BDNF serum may be caused by the acute exercise effect. Exercise can involve muscle activities in affecting BDNF level changes. Exercise reduces the blood glucose level and activates AMP-activated protein kinase (AMPK) to control blood glucose by stimulating the liver to synthesize ketone body D- $\beta$ -hydroxybutyrate (DBHB). DBHB synthesis will circulate to the brain via Blood-Brain Barrier (BBB), inducing increased BDNF expression by inhibiting Histone Deacetylase 2 (HDAC 2) and Histone Deacetylase 3 (HDAC 3) in the hippocampus ([Sleiman et al., 2016](#)).

Exercise is proven to increase cognitive functions by the increased BDNF level parameter, both in trial animals and humans ([Marquez et al., 2015](#)). BDNF is correlated with cognitive functions with a positive direction, where increased cognitive functions will be followed by increased BDNF level and vice versa ([Atake et al., 2018](#)). [Zhang et al. \(2015\)](#) reported that a low BDNF level is associated with decreased cognitive functions. Other researchers reported that increased BDNF expression in the brain might inhibit cognitive functional degradation ([Buchman et al., 2016](#)). It is because BDNF has a vital role in neuroprotective through a mechanism (neurogenesis, cellular survival, axonal growth, dendritic growth, and synaptic plasticity) activated via the link of BDNF and tropomyosin receptor kinase B (TrkB) ([Konishi et al., 2019](#)).

This study has limitations comprising 1) a small sample size divided into two groups, and hence, future studies are expected to use a bigger sample size and adding another comparison group such as high- and low-intensity exercises, 2) only applying one parameter examination (BDNF), where future studies are recommended to add other parameters from neurotrophic factors, such as neurotrophin-3 (NT-3) and neurotrophin-4/5

(NT-4/5) since they act as predictors in supporting survival, development, and function of neuron in the brain, providing better increased physiological functions observed from molecular parameters, 3) providing acute exercise that only causes temporary physiological changes. A meta-analysis by [Dinoff et al. \(2016\)](#) reported that increased peripheral BDNF concentration only occurred temporarily and rebound to baseline after 15-60 minutes post-acute exercise. Thus, future studies are recommended to perform chronic exercise intervention.

## CONCLUSION

Based on the study results, it can be concluded that one moderate-intensity exercise session using a treadmill for 40 minutes/session in the morning increases the BDNF serum level in obese female adolescents.

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