Moderate intensity exercise decreases the circulating level of betatrophin and its correlation among markers of obesity in women

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Abstract

Objectives: Positive energy homeostasis due to over-nutrition and a sedentary lifestyle triggers obesity. Obesity has a close relationship with elevated levels of betatrophin and may increase the risk of developing metabolic syndrome. Therefore, lifestyle modification through a non-pharmacological approach based on physical exercise is the right strategy in lowering betatrophin levels. This study aimed to analyze the effect of moderate-intensity interval and continuous exercises on decreased betatrophin levels and the association between betatrophin levels and obesity markers in women.

Methods: A total of 30 women aged 20–24 years old were randomly divided into three groups. Measurement of betatrophin levels using Enzyme-Linked Immunosorbent Assay (ELISA). Data analysis techniques used were one-way ANOVA and parametric linear correlation.

Results: The results showed that the average levels of betatrophin pre-exercise were 200.40 ± 11.03 pg/mL at CON, 203.07 ± 42.48 pg/mL at MIE, 196.62 ± 21.29 pg/mL at MCE, and p=0.978. Average levels of betatrophin post-exercise were 226.65 ± 18.96 pg/mL at CON, 109.31 ± 11.23 pg/mL at MIE, 52.38 ± 8.18 pg/mL at MCE, and p=0.000. Pre-exercise betatrophin levels were positively correlated with age, BMI, FM, WHR, FBG, and PBF ($p \le 0.001$).

Conclusions: Our study showed that betatrophin levels are decreased by 10 min post-MIE and post-MCE. However, moderate-intensity continuous exercise is more effective in lowering betatrophin levels than moderate-intensity interval exercise. In addition, pre-exercise betatrophin levels also have a positive correlation with obesity markers.

Keywords: betatrophin; moderate-intensity exercise; myokine; obesity.

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Introduction

Obesity is a metabolic disease that is the third leading cause of death and has become a global epidemic [1, 2]. Obesity is already considered an epidemic and has now become a pandemic [3]. This is due to the prevalence rate of obesity experiencing a continuous increase in both developed countries and developing countries [1, 4]. It was estimated that 1.9 billion people over the age of 18 were overweight, and 650 million of who were obese comprising 11% of men and 15% of women [5], meaning that more than one-third of adults globally were obese [6]. If every year, the prevalence of obesity continues to increase, it is estimated that by 2025, the prevalence of obesity will be 18% of men and 21% of women [7]. Based on Basic Health Research (Riskesdas) in 2018 showed that the prevalence of obesity in Indonesia people aged over 18 years old had increased, which was 21.8%, the number was higher than in 2013 (14.8%) and in 2007 (10.5%) [8]. Meanwhile, the prevalence of obesity in children in recent decades has also increased worldwide [9, 10]. In 2016 estimated that the prevalence of obesity in the world in children and adolescents aged 5–19 years is 124 million people and 213 million people are overweight [11]. Based on previous data, it was also reported that more than 70% of adolescents worldwide have low levels of physical activity [12]. Physiologically, changes in lifestyle behavior, such as increased time sitting, lying down [13], and reduced desire to exercise are the causes of increased body weight and risk of obesity [14, 15].

Obesity increases the risk of developing metabolic syndrome, as obesity is associated with increased levels of total cholesterol, increased triglyceride and low-density lipoprotein (LDL) levels, and decreased levels of high-density lipoprotein (HDL) [16], so that obese individuals are susceptible to type 2 diabetes mellitus [17], hypertension [18], hypercholesterolemia [19], several types of cancer [20, 21], nonalcoholic fatty liver disease (NAFLD), and dyslipidemia [22]. In addition, obesity also causes the heart workload to increase, thus increasing the risk of cardiovascular disease [23, 24]. In the condition of obesity, there is also impaired insulin secretion by pancreatic β-cells caused by increased levels of betatrophin [25–28]. Elevated levels of betatrophin can also have an effect on the kidneys and female organs, resulting in kidney problems [29] and polycystic ovarian syndrome (PCOS) [30]. Excessive levels of betatrophin can also inhibit the performance of the lipoprotein lipase (LPL) enzymes [31, 32]. The stunted performance of LPL enzymes causes fat to be irreversible into an energy source [33], resulting in increased fat storage in adipocytes [34]. Increased fat storage in adipocytes is one of the causes of obesity [35, 36]. Therefore, the discovery of new solutions for obesity prevention is becoming a very important target to do and potential therapies with high visibility at a low cost for obesity prevention in the global community are urgently needed.

Over the past decade, several interventions have been made on how to tackle obesity and boost metabolism without increasing the activity of internal stressors in the body [37, 38]. Recent findings suggest that exercise may lower betatrophin levels in obese people [26, 27]. Physical activity is organized in exercise programs oriented to strength development, low-intensity fitness, or a combination of these two [39]. The design of a program must follow specific rules with regard to the exercise to be undertaken, as well as its intensity, duration, and frequency, in order to obtain benefits [39]. A research conducted by Abu-Farha et al. [26] reported that the combination of both moderate-intensity aerobic (30 min) and resistance exercises using either a treadmill or cycling (10 min) lowered betatrophin levels in obesity. Likewise, the study of Susanto et al. [37] proved that moderate-intensity exercise lowered betatrophin levels in nonprofessional athletes. However, a research conducted by Enteshary et al. [40] found different results in which betatrophin levels increased post-moderate-intensity exercise in women with Type 2 Diabetes (T2D). Thus, the fundamental impact of moderate-intensity exercise on decreasing betatrophin levels remains controversial. Therefore, the aim of the present paper was to elaborate the potential regulation of moderate-intensity exercise decreases the circulating level of betatrophin and its correlation among markers of obesity in women.

Materials and methods

Experimental design

This research is a real experiment with a research design of randomized pretest–posttest control group design. The total subjects participating in the study were 30 women aged 21.27 ± 0.25 years old with body mass index (BMI) of 28.82 ± 0.30 kg/m^2, blood pressure (systolic blood pressure 113.33 ± 1.30 mmHg; diastolic blood pressure 76.00 ± 1.23 mmHg), resting heart rate (RHR) of 75.57 ± 2.23 bpm, fasting blood glucose (FBG) of 90.23 ± 1.33 mg/dL, hemoglobin (Hb) of 14.99 ± 0.24 g/dL, and maximum oxygen volume (VO_{2max}) of 28.08 ± 0.66 mL/kg/min examined using astrand 6 min cycle test method. All subjects were examined both physically and psychologically. All subjects obtained information orally or in writing about the research. The subjects filled out and signed informed consent before participating in the research. All of our research procedures comply with the Declaration of the World Medical Association of Helsinki regarding the ethical conduct of research involving human subjects.

Exercise protocol

The exercise program was applied and supervised by professional officers from the Fitness Center of Malang Health Office. The subjects were randomly divided into three groups: CON (n=10, control without intervention), MIE (n=10, moderate-intensity interval exercise), and MCE (n=10, moderate-intensity continuous exercise). The MIE intervention was carried out by employing the subjects running on a treadmill with moderate intensity of 60–70% HR_{max} for 45 min with details of 5 min of warming up (50–60% HR_{max}), 35 min of core exercise (5 min of work (60–70% HR_{max}) interspersed with active recovery on the treadmill for 2.5 min (50–60% HR_{max}) performed 5 times a while, and 5 min of cooling (50–60% HR_{max}) [41–44]. The intervention was conducted at 07.00–09.00 am [45, 46] using a treadmill (Pulsar 4.0 HP Cosmos Sports & Medical, Nussdorf-Traunstein, Germany) [47]. Heart rate monitoring during exercise used a polar heart rate monitor (Polar H10 Heart Rate Sensor, Inc., USA). The research environment had a room temperature of 26 ± 1 ℃ and a room humidity level of 50–70% [48, 49].

Blood samples

Blood samples were collected from a 4 mL cubital vein after a 12 h overnight fasting [50, 51]. At the time of the blood draw, the subjects were in a lying position. Blood samples were taken at 30 min pre-exercise and 10 min post-exercise. At the time of pre-exercise and post-exercise blood draws, the subjects remained in a fasting condition but they were allowed to drink mineral water without calories to prevent dehydration. The blood was centrifuged for 15 min at a speed of 3,000 rpm. The serum was then separated and stored at −80 ℃ for analysis of betatrophin levels on the next day [51–53].

Blood analysis

Examination of betatrophin levels was conducted at the Laboratory of Physiology of the Faculty of Medicine, Universitas Brawijaya, Malang, using the enzyme-linked immunosorbent assay (ELISA) kit (Cat No. E11644h; EIAab Science Co., Wuhan) with a standard curve range of 78–5,000 pg/mL and betatrophin sensitivity levels in a kit of 32 pg/mL. FBG examination was carried out using Accu-Chek Performa (Roche, Mannheim, Germany) with mg/dL concentration unit, while Hb examination used Easy Touch (Easy Touch, Hsinchu, Taiwan) with g/dL concentration unit.

Anthropometric measurements and physical fitness

Body height measurements were conducted using a stadiometer (SECA, Chino, CA, USA). Measurements of obesity markers included body weight, body mass index (BMI), body fat percentage (PBF), and fat mass (FM) using TANITA Body Composition Analyzer DC3607601(2)-1604 FA (TANITA Corporation of America, Inc., Arlington Heights, IL, USA). Measurement of the waist to hip ratio (WHR) was conducted by calculating waist circumference (WC) divided by hip circumference (HC). Measurement of maximal oxygen volume (VO_{2max}) by the Astrand 6 min cycle test method was performed using a Monark 828 E Version 1010 ergo cycle (Monark, Vansbro, Sweden). Measurement of resting heart rate (RHR) was conducted using Beurer Pulse Oximeter (PO 30 Pulse Oximeter, Beurer North America LP, Hallandale Beach, FL, USA). Blood pressure was measured using an automated device OMRON (OMRON Model HEM-7130 L, Omron Co., Osaka, Japan) at the non-dominant arm 3 times consecutively with a 1–2 min interval between two measurements while the participants were in a seated position.

Statistical analysis

Statistical analysis was conducted using SPSS software version 17 (SPSS Inc., Chicago, IL, USA). The normality test was conducted using the Shapiro-Wilk test, while the homogeneity test used the Levene test. Different tests were conducted using paired sample T-Test, one-way ANOVA, and then followed by Tukey's honestly significant difference (HSD) post hoc test and linear correlation with Pearson product-moment model. Data were presented as the mean ± standard error of the mean (SEM). Significant will be considered with p value ≤0.05.

Results

The basic profiles of the samples are displayed in Table 1. Table 1 shows that the average characteristic data of the study subjects showed no significant differences in all parameters of each group (p≥0.05). The results of the analysis of betatrophin levels between pre-exercise and post-exercise in each group are presented in Figure 1.

Figure 1 shows that betatrophin levels between pre-exercise and post-exercise in the CON group had no change and tended to be the same, while in the MIE and MCE groups, there was a change and the betatrophin levels tended to decrease. Paired sample T-Test results in the CON group showed that there was no significant difference in average betatrophin levels between pre-exercise and post-exercise (200.40 ± 11.03 vs. 226.65 ± 18.96 pg/mL, (p-value=0.269)) (Figure 1). However, the MIE group showed significant differences in average betatrophin levels between pre-exercise and post-exercise (203.08 ± 42.48 vs. 109.31 ± 11.23 pg/mL, (p-value=0.046)) (Figure 1). Likewise, the MCE group showed significant differences in average levels of betatrophin between pre-exercise and post-exercise (196.62 ± 21.29 vs. 52.38 ± 8.18 pg/mL, (p-value=0.000)) (Figure 1). The results

Table 1: The basic profiles of the samples.

Parameter	Group			One way-ANOVA p-Value
	CON (n=10)	MIE (n=10)	MCE (n=10)	
Age, yrs	21.30 ± 0.30	21.50 ± 0.64	21.00 ± 0.33	0.734
Body height, m	1.57 ± 0.01	1.59 ± 0.02	1.55 ± 0.01	0.060
Body weight, kg	73.30 ± 1.80	73.33 ± 2.93	67.63 ± 1.56	0.123
BMI, kg/m^2	29.42 ± 0.40	28.81 ± 0.70	28.23 ± 0.38	0.281
PBF (%)	45.17 ± 1.14	42.40 ± 1.43	42.98 ± 0.61	0.199
FM, kg	35.66 ± 1.36	34.32 ± 2.49	31.87 ± 1.82	0.391
WHR	0.81 ± 0.01	0.81 ± 0.01	0.79 ± 0.01	0.420
Hb, g/dL	15.09 ± 0.57	14.97 ± 0.29	14.93 ± 0.39	0.964
FBG, mg/dL	91.90 ± 1.82	90.50 ± 2.49	88.30 ± 2.59	0.552
SBP, mmHg	115.00 ± 2.69	111.00 ± 1.79	114.00 ± 2.21	0.439
DBP, mmHg	78.00 ± 2.00	73.00 ± 2.13	77.00 ± 2.13	0.220
RHR, bpm	73.70 ± 3.73	77.30 ± 4.92	75.70 ± 3.05	0.815
VO_{2max}, mL/kg/min	27.40 ± 0.61	27.59 ± 1.29	29.24 ± 1.37	0.467

BMI, Body mass index; PBF, Percentage of body fat; FM, Fat mass; WHR, Waist to hip ratio; Hb, Hemoglobin; FBG, Fasting blood glucose; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; RHR, Resting heart rate; VO_{2max}, Maximum oxygen volume; CON, Control group; MIE, Moderate-intensity interval exercise group; MCE, Moderate-intensity continuous exercise group. One way-ANOVA. Data are presented as mean ± SEM.

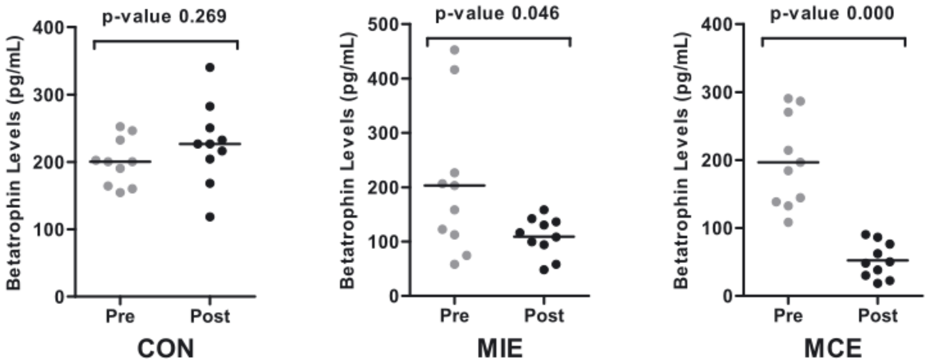

Figure 1: Pre-exercise vs. post-exercise betatrophin levels. CON, Control group; MIE, Moderate-intensity interval exercise group; MCE, Moderate-intensity continuous exercise group. Data are presented as mean ± SEM. p-Value was obtained using paired sample T-Test to compare post-exercise and pre-exercise betatrophin levels.

of the analysis of betatrophin levels in each group based on the time of blood collection can be seen in Table 2.

Table 2 of the One way-ANOVA test results shows that there was no significant difference in average betatrophin levels based on the timing of pre-exercise blood collection in each group ($p \geq 0.05$), while in post-exercise and delta (Δ) (Post–Pre), the results showed significant differences in average levels of betatrophin ($p \leq 0.001$). Tukey's HSD post hoc test results showed that there was a significant difference in average levels of post-exercise betatrophin between MIE and CON ($p \leq 0.001$), MCE and CON ($p \leq 0.001$), and MCE and MIE ($p \leq 0.05$). Likewise, delta (Δ) (Post–Pre) showed significant differences in average levels of betatrophin between MIE and CON ($p \leq 0.05$) and MCE and CON ($p \leq 0.001$), while MCE and MIE showed no significant difference ($p \geq 0.05$). The results of the correlation of pre-exercise betatrophin levels with obesity markers and characteristic parameters of the study subjects are shown in Figure 2.

Preliminary research results found a significant association of pre-exercise betatrophin levels with obesity markers and the characteristic parameters of study subjects including age and FBG. Pearson product-moment linear correlation parametric analysis showed that pre-exercise betatrophin levels were positively correlated with age ($r=0.557$, $p \leq 0.05$), BMI ($r=0.660$, $p \leq 0.001$), FM ($r=0.385$, $p \leq 0.05$), WHR ($r=0.543$, $p \leq 0.05$), FBG ($r=0.536$, $p \leq 0.05$), and PBF ($r=0.698$, $p \leq 0.001$).

Discussions

Obesity is a growing health problem in society globally and is associated with an increased risk of premature death [54]. Betatrophin is one of the newly identified proteins, mainly expressed in white adipose tissue (WAT), brown adipose tissue (BAT), and liver [55]. Evidence currently developing suggests that betatrophin plays an important role in metabolism, including the synthesis and degradation of lipids in cells, adipocyte differentiation [54], and energy balance [27]. In addition, several interventions have been done on how to overcome obesity and increase metabolism without increasing the activity of internal stressors in the body. However, the fundamental impact of moderate-intensity exercises on decreasing betatrophin levels in individuals with obesity remains controversial.

Table 2: Betatrophin levels in each group based on the time of blood collection.

Time	Betatrophin, pg/mL			One Way-ANOVA p-Value
	CON (n=10)	MIE (n=10)	MCE (n=10)	
Pre-exercise	200.40 ± 11.03	203.07 ± 42.48	196.62 ± 21.29	0.978
Post-exercise	226.65 ± 18.96	109.31 ± 11.23*	52.38 ± 8.18*†	0.000
Delta (Δ) post–Pre	26.25 ± 22.31	−93.76 ± 40.64*	−144.24 ± 22.33*	0.001

One way-ANOVA, followed by Tukey's HSD post hoc test, was used to compare the differences among groups. Data are presented as mean ± SEM. *Significant vs. control group (CON) ($p \leq 0.001$). †Significant vs. moderate-intensity interval exercise group (MIE) ($p \leq 0.05$).

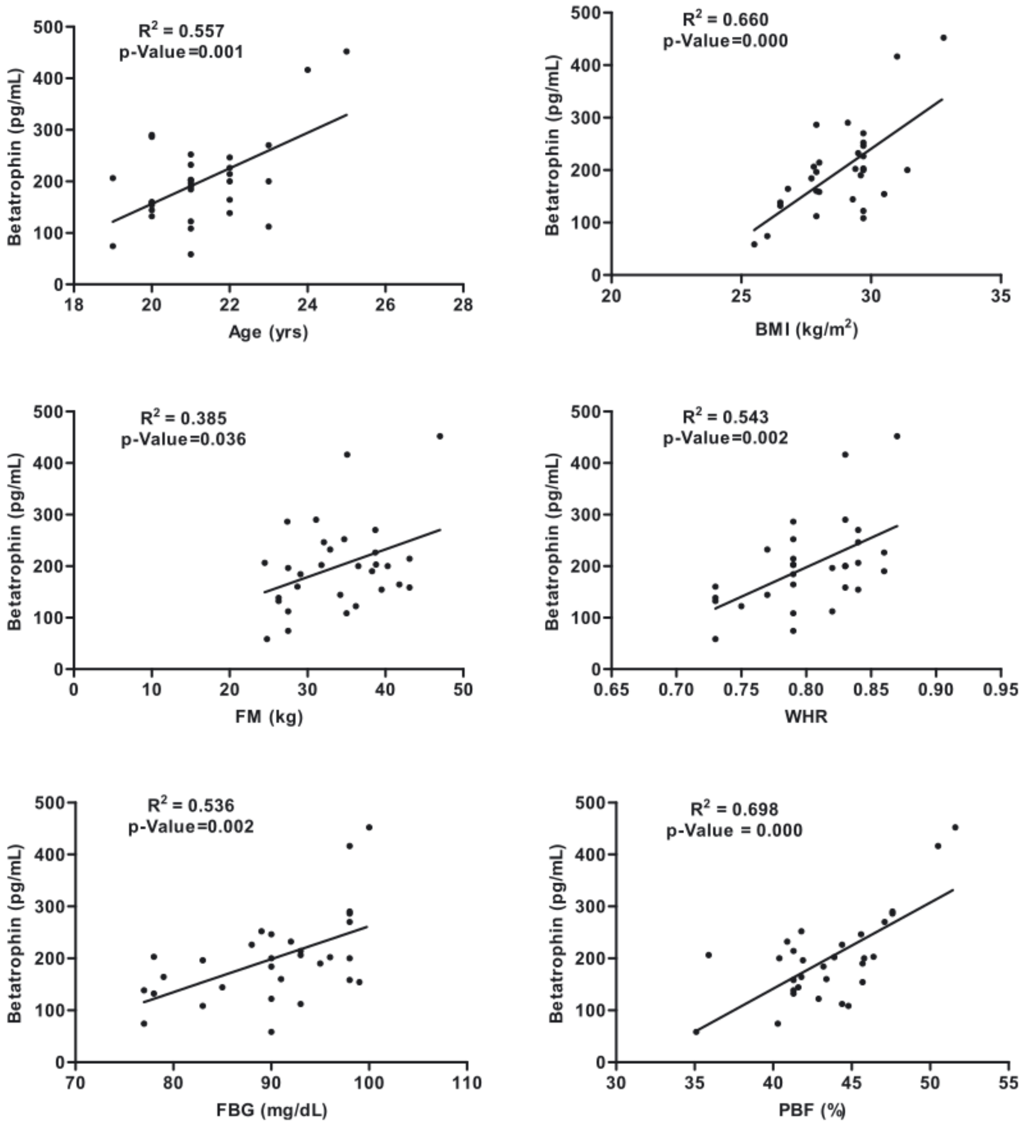

Figure 2: Correlation between pre-exercise betatrophin levels and obesity markers and the characteristic parameters of the study subjects. The significant linear correlation between parameters was visualized in the plot model (p≤0.05). *Significant with p≤0.05 by Pearson's product-moment correlation test. **Significant with p≤0.001 by Pearson's product-moment correlation test.

Therefore, we evaluated the effects of moderate-intensity interval exercise and moderate-intensity continuous exercise on decreasing betatrophin levels in obese women.

Our study demonstrated that there was no difference in betatrophin levels between pre-exercise vs. post-exercise on CON, while MIE and MIC showed significant differences in betatrophin levels between pre-exercise and post-exercise (Figure 1). The results were in line with the results of a study by Abu-Farha et al. [26] reporting that a combination of moderate-intensity aerobic exercise (30 min) and endurance exercise using a treadmill or cycling (10 min) significantly lowered betatrophin levels in obese subjects. Likewise, a research by Susanto et al. [37] reported that moderate-intensity exercise significantly lowered betatrophin levels in non-professional athlete subjects. The decrease in betatrophin levels is likely due to intervention factors (MIE and

MICE). At the time of intervention, there is an increase in the need for energy obtained from blood glucose, thus causing blood glucose levels to decrease. A research by Zheng et al. [56] reported that moderate-intensity aerobic exercise lowered blood glucose levels and improved glycemic control. Likewise, a study by van Dijk et al. [57] using obese subjects who were given moderate-intensity acute exercise interventions concluded that moderate-intensity acute exercise significantly lowered blood glucose levels. Decreased blood glucose levels can cause betatrophin secretion to decrease [58]. Zhang [59] reported that high blood glucose levels in obesity increase betatrophin secretion in the liver. Gusarova et al. [60] revealed that glycemic control in addition to avoiding hypoglycemia and hyperglycemia could also decrease excessive betatrophin expression.

Obesity is a condition where there is an excessive accumulation of body fat [21]. Excess fat in the body leads to increased triglyceride levels (hypertriglyceridemia) [28]. Increasement of triglyceride levels could stimulate betatrophin levels, so that obese individuals experience an increase in betatrophin levels [26, 27]. Elevated levels of betatrophin can inhibit the performance of the lipoprotein lipase (LPL) enzymes [31, 32, 59]. Inhibition of LPL enzymes makes triglycerides difficult to convert into energy [33]. In addition to having high levels of betatrophin, obese people also have high blood glucose levels [27, 61]. Meanwhile, the administration of acute exercise intervention with moderate-intensity requires glucose (glucose uptake) to be converted into energy (ATP) from carbohydrates, fats, and proteins [62]. Increased glucose uptake to be converted into energy makes glucose levels in the blood and betatrophin secretion decrease [58], so that acute exercise with moderate intensity can respond to the decrease in betatrophin levels in the body faster [26, 27].

The literature states that exercise can be used as a useful tool for the prevention, treatment, and rehabilitation of several diseases, such as diabetes mellitus and cardiovascular disease [39]. In diabetic patients exercise can be recommended and prescribed to manage blood glucose and improve the quality of general good health [13]. However, this recommendation must also take into account the lifestyle and habits of diabetics, so DM treatment should be carried out by a multidisciplinary team specializing in pharmacological aspects and physical exercise to increase the effectiveness of therapy [13]. In addition, an exercise that is prescribed and performed properly and correctly has also been shown to be safe and effective for people with cardiovascular disease [39].

Betatrophin is a newly discovered adipocytokine and is believed to play an important role in the body's metabolism [54]. Betatrophin is one of the main focuses in obesity research and relevant research results have been published continuously [26, 63]. Several epidemiological studies have shown that there is an independent relationship between circulating betatrophin levels and obesity [64–66], while other studies reported no association [63, 67–69]. Inconsistent results are likely due to too few subject counts and also influenced by many factors [54]. Therefore, we conducted a re-study to further evaluate the relationship between circulating betatrophin levels and obesity.

Our data present that betatrophin levels have a positive relationship with age, body mass index (BMI), fat mass (FM), waist-to-hip ratio (WHR), percentage of body fat (PBF), and fasting blood glucose (FBG) (Figure 2). The results confirm previous findings that reported that betatrophin levels were positively correlated with age, BMI, FBG [26, 33, 61, 70–72], WHR [34], FM [65], and percentage of body fat (FAT %) [70]. This association is likely due to an increase in obese individuals with elevated levels of betatrophin [27, 28, 63, 64, 67]. It is as evidenced by the results of a meta-analysis conducted by Ye et al. [54] which reported that betatrophin levels were higher in obese individuals compared to those in healthy individuals. Elevated levels of betatrophin can inhibit the performance of the LPL enzymes [31, 32]. The stunted performance of LPL enzymes causes fat to be irreversible into an energy source [70], resulting in increased fat storage in adipocytes [34].

Adipose tissue, known as an important endocrine organ, has attracted a lot of attention because it has many effects on several metabolic processes, such as glucose homeostasis, lipid metabolism, inflammation, and blood pressure [54]. Betatrophin is known as angiopoietin-like protein 8 (ANGPTL8), refeeding induced fat and liver (RIFL), chromosome 19 open reading frame 80 (C19ORF80), hepatocellular carcinoma-associated protein TD26, and lipasin, which is a new adipokine secreted from adipose and liver tissue [55]. Previous studies using mouse models implied an important role of betatrophin in some metabolic-related pathways, such as lipid metabolism and energy balance [26]. Based on a meta-analysis of 9 observational studies, individuals with obesity have higher levels of betatrophin than normal-weight individuals [54]. There is emerging evidence supporting a positive association between betatrophin levels and obesity [26, 54, 65, 66]. *In vitro* studies conducted by Ren et al. [73] showed that betatrophin expression increased more than 100-fold during cell adipogenesis 3T3-L1. Its knockout in 3T3-L1 cells during adipogenesis and its knockdown lead to a decrease in adipogenesis. Furthermore, betatrophin expression increased about 8 times in white adipose tissue (WAT) in obese model mice compared to wild mice [74]. Likewise, betatrophin mRNA is expressed very highly in humans with obesity [26]. High concentrations of betatrophin in circulation can directly increase the risk of obesity in adults [54]. Therefore, betatrophin can serve as a viable therapeutic target in the fight against obesity in adults.

There are some limitations to this study. First, the number of subjects who participated in this study was still relatively small who met the inclusion criteria and participated in the training program. Thus, a large number of samples may be needed to further analyze the effect of moderate-intensity exercise on the modulation of betatrophin levels in obese women. Second, the type of exercise intervention for this study is a single intervention (acute exercise), several possible types and intensity of exercise can affect the regulation of betatrophin. Therefore, further research is needed on the type and intensity of exercise. Third, circulating betatrophin levels can be influenced by gender and lipid profile, so further research can add to the examination of body fat profiles, such as total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and comparing betatrophin levels between men and women.

Conclusions

Taken together, the results of this study showed that moderate-intensity interval exercise and moderate-intensity continuous exercise performed for 30–35 min lowered betatrophin levels. However, moderate-intensity continuous exercise is more effective in lowering betatrophin levels compared to moderate-intensity interval exercise. Therefore, moderate-intensity continuous exercise can be a major modality in lowering betatrophin levels and betatrophin can serve as a promising therapeutic target for obesity in adults. Further research is needed to explore in more detail the physiological mechanisms of exercise in lowering betatrophin levels in obesity.

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Competing interests: Authors state no conflict of interest.

Informed consent: Informed consent was obtained from all individuals included in this study.

Ethical approval: Based on the ethical standards of the Declaration of Helsinki 1975, this study has been approved by the Health Research Ethics Commission of the Faculty of Medicine, Universitas Airlangga, Surabaya with registration number: 309/EC/KEPK/FKUA/2019.

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