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Original article

# Dynamic alteration of plasma levels of betatrophin in younger female onset obesity post acute moderate-intensity exercise training

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ABSTRACT

Obesity is a global metabolic disease anchored by a lack of physical activity lipid disturbances. Hitherto, betatrophin is a potential liver-derived hormone that regulates lipid metabolism. A total of 26 selected onset obese individuals (BMI range ± 28–31) were enrolled in this study and given moderate-intensity exercise. Importantly, our data show that acute moderate-intensity interval exercise (MIIE) and acute moderate-intensity continue to exercise (MICE) for 40 min significantly decrease the plasma level of full-length betatrophin respectively (174.18 ± 48.19 ng/mL; 182.31 ± 52.69 ng/mL), compared to the placebo (283.97 ± 32.23 ng/mL) post 10 min and 6 h exercise treatment ($p \leq 0.05$). The plasma level of betatrophin was significantly and negatively correlated with BMI ($r = -0.412$, $p = 0.037$), fasting blood glucose ($r = -0.390$, $p = 0.049$), and positively correlated with $VO_{2max}$ ($r = 0.456$, $p = 0.019$). In addition, the linear and ordinal logistic regression analysis shows that betatrophin, is a potential predictor for BMI [estimate value = 0.995, p = 0.037 and OR (95 % CI) = 0.992 (0.0984–1.00), p = 0,048]. In summary, our data demonstrate that the circulating levels of betatrophin were decreased after acute moderate-intensity exercise training.



## 1. Introduction

Higher occurrence of obesity in Southeast Asia countries is a future challenge for community health management in the region (Ohta et al., 2019). Permanent obesity and sedentary lifestyle-linked physical inactivity are essential contributors to gastrointestinal cancer in the Asia-Pacific (Ko et al., 2018). Empirical evidence has shown that parental feeding practices and unhealthy eating behaviors were significantly correlated with overweight and obesity in this area (Lindsay et al., 2017; Song et al., 2020). Importantly, overweight and obesity are severe problems, in particular for the Indonesian population since both of these metabolic disorders are observed in urban or even rural areas (Rachmi et al., 2017). Thus, this problem could be a potential trigger for health management against overweight obesity and metabolic diseases. The development of drugs and nondrug interventions to prevent overweight obesity progression may include emergence.

Dyslipidemia is potentially involved in obesity and type 2 diabetes mellitus (T2DM) risk (Klop et al., 2013; Ren et al., 2017; Carpentier, 2015; González-Muniesa et al., 2017). Importantly, it has been established that liver-derived hormones (betatrophin/lipasin/C19orf80/ANGPTL-8) may contribute to obesity incidence-related triglyceride metabolism. Betatrophin may induce obesity through increasing the circulating levels of triglyceride and even its deposit within the adipose tissue. Betatrophin is a regulator of triglyceride levels and acts through lipoprotein lipase activity in the vascular wall (Fu et al., 2014; Zhang, 2016; Gao et al., 2015; Tseng et al., 2014) or even in the cell culture level (Sertogullarindan et al., 2019; Xu et al., 2019; Hassan et al., 2019). Interestingly, betatrophin is strongly correlated with overweight,

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obesity, glucose intolerance, and T2DM (Fu et al., 2014; Fenzl et al., 2014; Hu et al., 2014; Zhang et al., 2014; Abu-Farha et al., 2018; Liu et al., 2018; Gómez-Ambrosi et al., 2016; Ye et al., 2019; Wu et al., 2016; Guo et al., 2015; Rejeki et al., 2022). Moreover, the significant changes of this liver-derived hormone correlate with cancer development (Wang et al., 2016), kidney dysfunction (diabetic nephropathy) (Chen et al., 2016), and colorectal cancer (Susanto et al., 2019). The downregulation of betatrophin disrupts triglyceride metabolism without any significant alteration on glucose homeostasis (Wang et al., 2013). The restriction diet in obese/overweight adults significantly decreases the level of betatrophin (Hu et al., 2019). Therefore, the specific intervention on betatrophin activity may become a fundamental approach for obesity prevention and its related physiological disorders.

Empirically, individual or community health management on overweight and obesity has been done by drug treatment, daily intake or diet programs, and physical training or exercise (Karaman et al., 2022; Sugiharto et al., 2022; Ruiz et al., 2019; Hunter, 2019; Golbidi et al., 2012; Bianchi et al., 2007). The regular program combating overweight and obesity is not only the clinician's responsibility but also should be supported by community intensive or frequent activities. Non-drug treatment by physical exercise can improve metabolism, decrease metabolic stress, attenuate obesity development, and maintain the circadian cycle of the human body (Karaman et al., 2022; Gabriel & Zierath, 2019; Geng et al., 2019; Zhang et al., 2019). The in vivo model of high-intensity exercise improves lipid and blood glucose metabolism by involving betatrophin and irisin (Amri et al., 2019). In a prior study, it was proclaimed that moderate-intensity calisthenics concurred with slow rhythm musical therapy alleviated the circulating betatrophin level (Susanto et al., 2020). Likewise, anaerobic exercises have positive effects on glucose balance by regulating betatrophin levels (Karaman et al., 2022). Moreover, the long-term physical training program reduced the plasma level of betatrophin in individuals with obesity (Abu-Farha et al., 2016). However, even though the physical activity intervention could be used as an alternation solution to overweight and obesity, discrepancies consistently exist. High-intensity physical exercise can trigger inflammation in individuals with metabolic syndrome (Steckling et al., 2019) and corroborate the metabolic process within the human body (Nylén et al., 2019). Therefore, the save, low cost, and novel physical training programs to combat obesity are required. The design of this study was to appraise the circadian profile of circulating betatrophin level in individuals with early-onset obesity medicated with short-term moderate-intensity calisthenics.

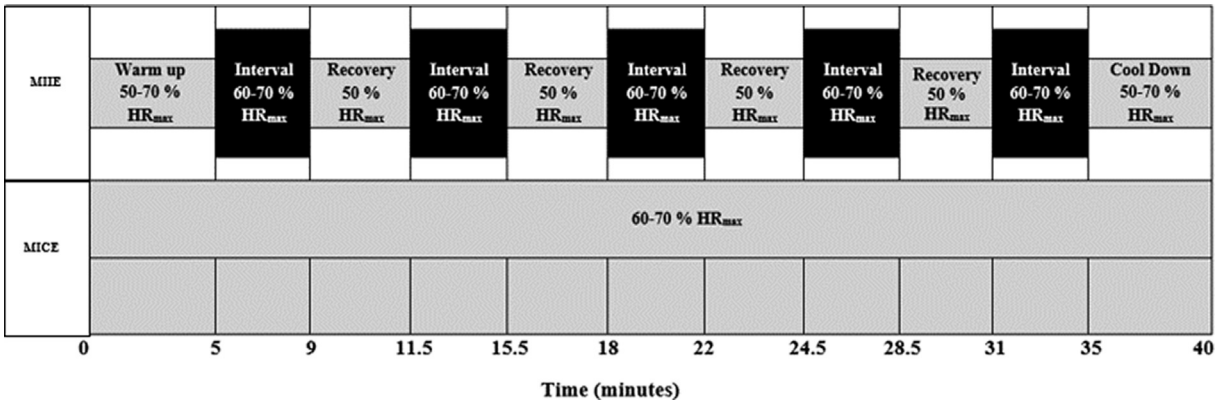
## 2. Materials and methods

### 2.1. Samples

The Institutional Review Board (IRB), Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia, acquiesced the legal acquiescence for this experimental investigation (ethics number:26/EC/KEPK-S1/02/2020). Preceding the calisthenics program, participants were probed to supplement an notified concordance form based on the Helsinki Declaration of 1975. The experimental groups were detached into three classification, comprising high-intensity to moderate-intensity calisthenics with interval (MIIE), and moderate-intensity calisthenics towards the continuous model (MICE). This study embedded a total of 26 young female student onset obesity subjects. The inclusion criteria was individuals age of 18–25 years old, body mass index (BMI) > 25 kg/m$^2$, normal systolic and diastolic blood pressure 120–100/100–80 mmHg, resting heart rate (RHR) of 60–100 beats/minute, Hemoglobin levels of 13–18 g/dL, fasting blood glucose (FBG) level $\leq$ 100 mg/dL, the percentage of body fat mass $\geq$ 30 %, and $VO_{2max}$ (maximal oxygen volume) 35–45 mL/kg/min. The subjects were verified without smoking history, non-alcoholic consumption, non-hypertension, and nondiabetic. Moreover, the participants had not an illness with personal-based therapy by specific medical intervention. Blood samples were obtained during the mid-follicular phase of the menstrual cycle after at least 12 h of nocturnal fasting (Qu et al., 2017). After the selection of the samples, twenty-six students were recruited to participate in the physical exercise treatment.

### 2.2. Acute moderate-intensity exercise intervention

The physical exercise treatment was implemented also administered by the sports center proficient coaches from the sports major faculty, Universitas Negeri Malang, Indonesia. The individuals from each group were monitored to avoid heavy physical exercise for 24 h before the physical exercise intervention. The physical exercise intervention was given at 6:30 to 10:30 a.m. Before the treatment begin, all participants were then going to a medical check and followed by the first blood collection (zero minute serological sample collection) after overnight fasting. Therefore, post the first blood collection the subject was given oral water containing 5 % glucose to prevent the risk of hypoglycemia (Parker et al., 2017). The subject were then took a recovery step for 30 min (Tsuchiya et al., 2018).



Further treatment with moderate-intensity interval exercise (MIIE) and moderate-intensity continuous exercise (MICE) was carried out by warming up the step through running on a treadmill (Richter Treadmill Semi-Commercial-Evolution (4.0 HP DC; Richter Fitness, Taipei, Taiwan) with Inclination level of 0 %) for five minutes ($HR_{max}$ 50–70 %). The method used in determining $HR_{max}$ is using the formula: $HR_{max}$ – age in years (220 - age in the year) (Tsuchiya et al., 2014; Santos et al., 2019; Sugiharto et al., 2022). This step was conducted at room temperature (22–25 °C) with the standard humidity level 50–70 % (Santos et al., 2019; Qiu et al., 2018). The interval moderate-intensity exercise was set up by running on a treadmill for 40 min ($HR_{max}$ 60–70 %) (Rejeki et al., 2021). The physical exercise for the interval model was separated into 5 min warm-up, with a rest period of 2.5 min (ratio of work to rest 1:1/2 and $HR_{max}$ 50 %) with five times replication. On the other hand, the continuous model was conducted by running low intensity on a treadmill for 40 min ($HR_{max}$ 60–70 %) (Tew et al., 2019). The heart rate was monitored during exercise using a polar heart rate monitor (Polar H 10 Heart Rate Sensor, USA. Inc). In the final step for both this exercise treatments, the participants were done running on a treadmill ($HR_{max}$ 50–70 %) for five minutes.

### 2.3. Serological analysis

The blood pattern were obtained periodically in the preexercise step (30 min before the physical training), 10 min, 6 h, and 24 h post physical intervention, respectively. Blood samples were acquired from peripheral venous and collected within vacutainer EDTA tubes. After the centrifugation process, the plasma samples were then stored in the fridge with temperature −80 °C. The serological plasma parameters were quantified utilizing the systematized procedure of COBAS MIRA sequence. Nevertheless, a human ELISA kit for lipasin either betatrophin was utilized to quantify the full-length betatrophin circadian level (EIAab lab, China, catalog No. E11644h). Age, weight, height, BMI, BMR, fat mass, muscle mass, systolic blood pressure, and diastolic blood pressure were all quantified by means of physical, physiological, and anthropometric.

### 2.4. Statistical analyses

The normality test with the Kolmogorov-Smirnov archetype was utilized to scrutinize the data dispersion. A parametric One-way ANOVA test was implemented to equate data per all groups. The parameters or variables associations were substantiated by undeviating interdependence with the Pearson product-moment pattern, univariate undeviating regression, and ordinal logistic regression analysis was performed. The significant level was considered 5 %, and the data were exhibited as mean ± SE.

## 3. Results

The baseline biochemical characteristics of the parameters among groups were documented in Table 1 and Fig. 1. The subject's age, body mass index (BMI), Hemoglobin, fasting blood glucose, basal metabolic rate (BMR), waist and hip circumference, fat mass, percent body fat, muscle mass, $VO_{2max}$, heart rate, systolic blood pressure (SBP), and diastolic blood pressure (DBP) are not significantly different compared to the placebo ($p \geq 0.05$). Interestingly, the early symptom of diabetes mellitus was found in all groups. Furthermore, predicated on our preparatory pronouncements, an eloquent interdependence betwixt betatrophin and several imperative metabolic syndrome parameters was ascertained (Table 2). The Pearson product-moment undeviating interdependence parametric analysis ascertained that the betatrophin plasma level was substantively and contrarily concatenated with BMI ($r = -0.412$, $p \leq 0.05$) and fasting blood glucose ($r = -0.390$, $p \leq 0.05$), while substantively correlated with $VO_{2max}$ ($r = 0.456$, $p \leq 0.05$). There was no eloquent correlation betwixt betatrophin and other parameters (Table 2).

Central to this issue is that the preliminary data of this study have shown that the 24 h physiological profile of betatrophin levels indicates an interesting pattern during the physical exercise model (Fig. 2). The circulating level of betatrophin were not significantly different among groups (pre-exercise program). However, the plasma level of betatrophin was significantly decreased after 10 min of treatment compared to the control group. This similar profile was continued until six hours of post-moderate-intensity exercise in both interval and continuous groups. In the last stage of the serological screening, after 24 h of physical training, the circulating level of betatrophin is gradually returned to the baseline level and It does not differ considerably betwixt groups.

The regression analysis shows that betatrophin has a correlation with BMI and $VO_{2max}$ (Table 3 and Table 4). Betatrophin is a significant predictor for BMI ($p \leq 0.05$) by linear regression and binary logistic regression analysis (the parameter estimate, and OR are all positive). This data implies that feedback value stretches when betatrophin levels escalate, and vice versa. Based on this preliminary data, betatrophin (X) could be a significant predictor for BMI ($p \leq 0.05$).

**Table 1**
Baseline characteristics of the study population from different groups.

| Parameters | Control | MIIE | MICE |
|---|---|---|---|
| Age (yrs) | 20.75 ± 0.36 | 20.89 ± 0.51 | 20.67 ± 0.23 |
| BMI ($kg/m^2$) | 29.55 ± 0.62 | 28.48 ± 0.65 | 28.61 ± 0.56 |
| Muscle Mass (kg) | 38.45 ± 1.28 | 41.21 ± 2.51 | 37.58 ± 0.88 |
| Fat Mass (kg) | 34.85 ± 2.30 | 29.91 ± 2.14 | 31.29 ± 1.64 |
| Percent Body Fat (%) | 45.77 ± 1.33 | 41.37 ± 1.80 | 43.72 ± 0.89 |
| Waist Circumference (cm) | 91.75 ± 4.78 | 84.78 ± 2.64 | 86.56 ± 3.02 |
| Hip Circumference (cm) | 106.62 ± 2.17 | 106.44 ± 2.35 | 107.33 ± 1.95 |
| BMR (kcal) | 1369.38 ± 49.96 | 1421.78 ± 69.34 | 1325.00 ± 33.47 |
| $VO_{2max}$ (mL/kg/min) | 27.21 ± 0.74 | 27.61 ± 1.44 | 29.63 ± 1.47 |
| Heart Rate (Beats.min) | 38.45 ± 1.28 | 41.21 ± 2.51 | 37.58 ± 0.88 |
| SBP (mmHg) | 113.75 ± 1.83 | 112.22 ± 1.47 | 112.22 ± 1.47 |
| DBP (mmHg) | 76.25 ± 1.83 | 74.44 ± 1.75 | 75.56 ± 1.75 |
| Hemoglobin (g/dL) | 15.76 ± 0.66 | 15.62 ± 0.46 | 15.41 ± 0.31 |
| Fasting Glucose Level (mg/dL) | 91.00 ± 2.36 | 90.00 ± 2.09 | 88.22 ± 2.74 |

The SBP = systolic blood pressure, DBP = diastolic blood pressure, fasting glucose level, Hemoglobin, BMR = Basal Metabolic Rate. One Way-ANOVA, followed by Tukey's posthoc test, was used to compare the differences among groups. Data are presented as mean ± SE. * Significant value of each parameter compared to placebo ($p \leq 0.05$).

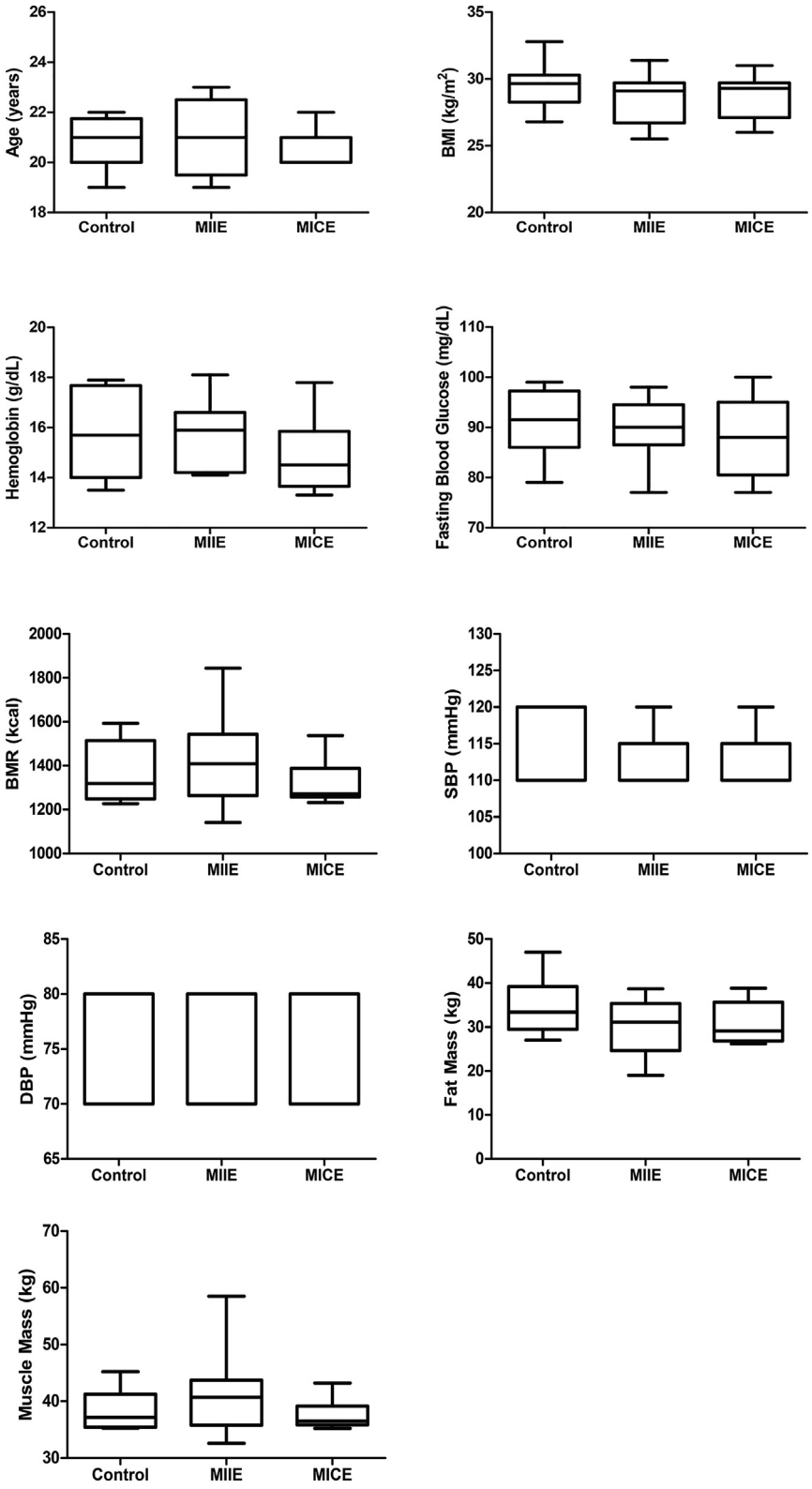



**Fig. 1. Box-Plots Model for the Differences between Groups.** * Significant vs placebo ($p \leq 0.05$).

## 4. Discussion

The general hypothesis in this study was that acute moderate-intensity exercise could affect the circulating level of betatrophin. Betatrophin/ANGPTL-8/lipasin is a hormone that is predominantly expressed in the liver. ANGPTL-8/Betatrophin is an essential hormone that regulates lipid and its metabolism, especially triglycerides (Zhang et al., 2014; Abu-Farha et al., 2018; Gómez-Ambrosi et al., 2016; Wang et al., 2013; Zheng et al., 2020). Numerous studies also showed that betatrophin has been highly identified and targeted in patients with obesity or diabetes mellitus (Zheng et al., 2020; Abu-Farha et al., 2016; Li et al., 2016; Yi

et al., 2015). Therefore, this hormone can be proposed as a potential endocrinal target in applying physical treatment to overweight obesity development. Consistent with that, this physical exercise program's results exhibited that moderate-intensity exercise therapy had a favourable effect on the betatrophin profile in obese person. The moderate-intensity physical training program in our study can also stimulate the muscle metabolic-related marker irisin and thermogenesis-related protein PGC-1α concentration despite reducing circulating level of the metabolic stress hormone cortisol and malondialdehyde level. Several studies in obese subjects were shown that modified treatments like diet, exercise, or a combination of three to twelve months in which the influence of lifestyle changes on betatrophin concentrations were assessed (Abu-Farha et al., 2016; Roth et al., 2017; Crujeiras et al., 2016). The results demonstrated that a short duration practice program showed that betatrophin levels decreased significantly in 62 obese subjects than 82 non-obese subjects following a combination of moderate aerobic strength and resistance formation (Abu-Farha et al., 2016).

The application of physical exercise is one of the preventing approaches against overweight progress to obesity. It was predicted that the intervention by this exercise would affect the physiological performance, particularly in individual onset obesity. The maintenance of a high physical exercise level significantly reduces weight gain, especially among women. In comparison with those who were continuously inactive, active individuals gain weightlessly over the next period (Wiklund, 2016). In a similar vein, high-quality studies showed that daily physical activity involvement enhances the regulation of blood glucose and can reduce hepatic lipid content or postpone type 2 diabetes, as well as have a beneficial effect on lipids, blood pressure, cardiovascular events, mortality, and quality of life (Colberg et al., 2010; Johnson et al., 2009). Therefore, the administration of this physical training program was significantly perceived to become the baseline model combating obesity and its related diseases. Significantly, the previous study has shown that moderate-intensity continuous exercise (MICE) could induce the better performance of circadian rhythm and cardiac activity in young age with overweight/obesity (Abu-Farha et al., 2016).

A growing number of studies have recently focused on the relationship between betatrophin and obesity. However, the accumulated data showed inconsistent and controversial findings. Specifically, the research found that serum betatrophin levels were substantially higher in overweight patients but not in obese patients (Guo et al., 2015). In contrast, another study disclosed that betatrophin levels were comparable in obese and insulin-resistant as well as in non-obese subjects (Battal et al., 2018), while another study indicated that betatrophin levels in obese were higher than in non-obese people (Abu-Farha et al., 2016). The serum levels of ANGPTL8/betatrophin/lipasin are significantly increased in obese patients compared to lean individuals independently to the present of polycystic ovary syndrome (Keyif et al., 2020). Furthermore, other studies portrayed that betatrophin increases in both overweight and obese subjects (Fu et al., 2014; Borniger et al., 2013). The circulating betatrophin/ANGPTL8 levels were significantly correlated to body fat distribution (visceral/subcutaneous adipose tis-

**Table 2**
Univariate correlations with plasma betatrophin in all participants.

| Parameters | Betatrophin | |
|---|---|---|
| | r | p-value |
| Age (yrs) | 0.272 | 0.179 |
| BMI (kg/m$^2$) | −0.412 | 0.037* |
| Muscle Mass (kg) | 0.096 | 0.640 |
| Fat Mass (kg) | −0.244 | 0.229 |
| Percent body fat | −0.252 | 0.214 |
| Waist Circumference (cm) | −0.090 | 0.661 |
| Hip Circumference (cm) | −0.247 | 0.224 |
| BMR (kcal) | 0.012 | 0.955 |
| $VO_{2max}$ (mL/kg/min) | 0.456 | 0.019* |
| Heart rate (beats/min) | −0.236 | 0.245 |
| SBP (mmHg) | 0.003 | 0.987 |
| DBP (mmHg) | −0.146 | 0.476 |
| Hemoglobin (g/dL) | 0.173 | 0.399 |
| Fasting Glucose Level (mg/dL) | −0.390 | 0.049* |
| Irisin (ng/mL) | −0.050 | 0.824 |
| PGC-1α (ng/mL) | −0.048 | 0.833 |

* Significant with $p \leq 0.05$ by Pearson product-moment correlation test.

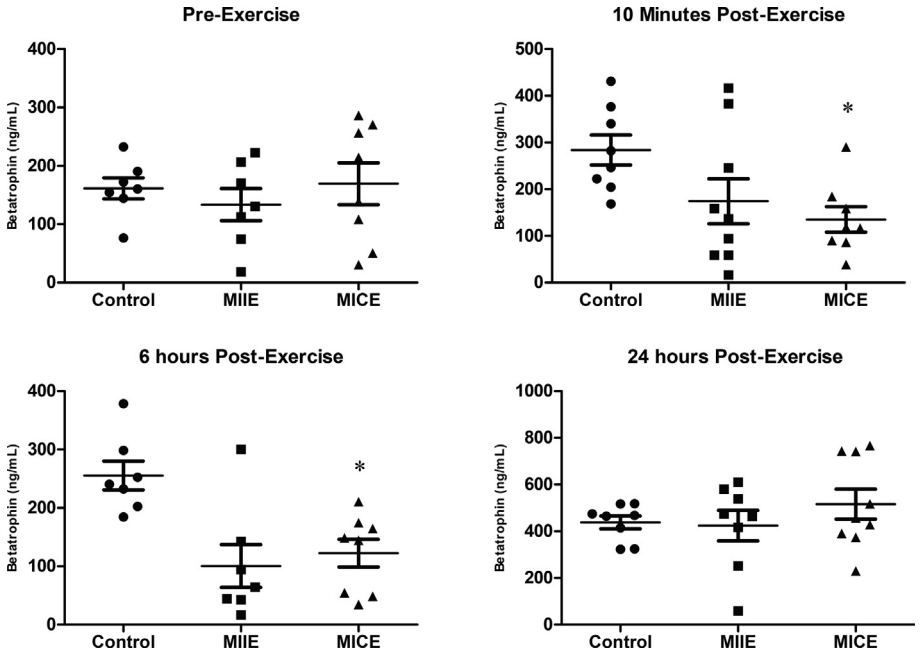



**Fig. 2. The circulating levels of betatrophin pre and post the physical exercise program.** * Significant vs placebo ($p \leq 0.05$).

**Table 3**
Univariate linear regression analysis.

| Response | Predictor | Estimate | p-value |
|---|---|---|---|
| BMI | Betatrophin | 0.995 | 0.037* |
| FBG | Betatrophin | 0.980 | 0.049* |
| $VO_{2max}$ | Betatrophin | 1.013 | 0.019* |
| Irisin | Betatrophin | 1.003 | 0.305 |
| PGC-1α | Betatrophin | 1.000 | 0.833 |

* Significant with $p \leq 0.05$.

**Table 4**
Binary logistic regression analysis.

| Response | Predictor | OR (95 % CI) | p-value |
|---|---|---|---|
| BMI | Betatrophin | 0.992 (0.984–1.000) | 0.048* |
| BMI | Irisin | 1.342 (0.419–4.300) | 0.621 |
| BMI | PGC-1α | 1.011 (0.505–2.027) | 0.975 |

* Significant with $p \leq 0.05$.

sue ratio) in normal glucose tolerance subjects (Zheng et al., 2020). Moreover, it was hypothesized that these correlations were associated with the fundamental function of betatrophin to regulate triglycerides. These phenomena give little insight regarding the plasma level of betatrophin, which negatively correlates with BMI and fasting blood glucose in young female onset obesity. Thus, we expect that there are other possible cofactors that may contribute to the expression of betatrophin in particular conditions.

Additionally, in the present study, we showed a positive correlation between betatrophin and $VO_{2max}$ in obese subjects. It has been reported that both betatrophin and $VO_{2max}$ were increased during exercise (Lundsgaard et al., 2018; Sanchis-Gomar & Perez-Quilis, 2014); however, the specific correlation between the expression of betatrophin and $VO_2$ remains unknown. Moreover, as per total body oxygen consumption increases in the obese subject (Kress et al., 1999), it might improve the metabolic rate, especially on fatty acids and triglycerides metabolism. These parts may become the main reason for the rising expression of betatrophin during exercise due to its novel function in controlling fatty acids and triglycerides metabolism (Sertogullarindan et al., 2019).

On the other hand, the data of MIIE and MICE treatment on obese subjects demonstrating the circulating level of betatrophin were significantly decreased at ten minutes and six hours post physical exercise program compared to the control ones. Previously, Sanchis-Gomar & Perez-Quilis (2014) in their review study, postulated that exercise should increase betatrophin expression. The proposed mechanism of action starts when exercise triggers ROS to activate p38MAPK. Together, p38MAPK activation regulates the expression of PGC-1α. The downstream effect of PGC-1α activation induces the secretion of irisin through FNDC5 expression. The secreted irisin then acts on white adipose cells and promotes the activation of UCP1. The expression of UCP1 induces the secretion of betatrophin, regeneration of β-cells, and decreases insulin resistance. In addition, the interesting findings from a previous studies mentioned that betatrophin knockdown could enhance beiging and mitochondrial biogenesis in white adipocytes through activated AMPK signaling pathway (Liao et al., 2020). In contrast with this theory, the study conducted by Gómez-Ambrosi et al. (2016) in 153 subjects demonstrated that the concentration of circulating betatrophin was significantly suppressed in obese normoglycemic patients (40 %), obese patients with impeded glucose permissiveness (59 %), and obese patients indicated second type diabetes mellitus (70 %) (Ren et al., 2012). The mechanisms of action on how betatrophin decreases after exercise are still unclear. However, Gómez-Ambrosi et al. (2016) study suggested that the possible variety of inflammation might have a different effect on affecting betatrophin expression because it influences the metabolism of both glucose and lipids. Additionally, in their case, obese subjects with type 2 diabetes mellitus have been diagnosed recently, while in other studies, the patients showed to have a more extended history of diabetes. In relation to our findings, which showed that betatrophin expression was elevated in the 24 h postexercise, we hypothesized that obese subjects have an uncontrolled amount of food intake after six hours postexercise. In conformity with Ren et al. (2017) substantiated that betatrophin transcript level in white adipose tissue (80-fold) and liver (12-fold) is dramatically increased after refeeding the fasted mice.

Collectively, the preliminary finding of this study provides a theoretical framework that acute moderate-intensity exercise with a continuous and interval models might be a future exercise model for combating obesity-related triglycerides and liver-derived hormones. However, our scrutinization has several flaws. This non-clinical investigation cannot stipulate circumstantial dossier for the whole serological parameters, mainly circulating marker-correlated lipid metabolism. Moreover, our exercise model only addressed specific gender with limited samples and cannot accommodate both sexes. However, the use of obese female samples must consider the menstrual cycle and it is recommended that blood samples be taken in the mid-follicular phase so as not to affect the results of the study. En masse, this physical training paradigm may also be utilized to a young person who has conceived obesity.

## 5. Conclusion

To sum up, the data of this study have indicated that the short-term treatment of individual onset obesity by moderate-intensity training altered the circadian plasma profile of full-length betatrophin. The plasma level of betatrophin was increased in young female onset obesity and decreased during the physical training intervention. The plasma level of betatrophin shows a significant correlation with BMI and body endurance-related oxygen consumption. Hence, our study highlights the potential future therapeutic model of reducing betatrophin level through moderate-intensity physical exercise programs in subjects with obesity.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Authors' contribution

HS conceived the research and contributed to the research project design, data analysis, data interpretation, and manuscript writing. S and AP contributed to research project design, data collection, and data analysis. AT contributed to data interpretation and report of the paper. JDTP contributed to the statistical analysis and manuscript preparation.

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