Research Article

Moderate-Intensity Exercise and Musical Co-Treatment Decreased the Circulating Level of Betatrophin

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Introduction. In general, the significant contribution of lack of physical activity is strongly correlated with lipid metabolism and metabolic disorder. Hitherto, betatrophin is a potential hormone that regulates the lipid profile in the body circulation-associated triglyceride level. This study was designed to evaluate the alteration of betatrophin levels in subject-onset hypertriglyceridemia with exercise intervention co-treated with music. **Materials and Methods.** A total of 60 nonprofessional athletes were enrolled in this study and given moderate-intensity exercise (MIE) combined with middle rhythm musical co-treatment. The ELISA method was applied to quantify the serum level of betatrophin in all samples. The statistical analysis was performed by applying the Kolmogorov-Smirnov normality test, one-way ANOVA, and parametric linear correlation and regression. **Results.** Interestingly, our data show that MIE decreased the circulating level of betatrophin combined with music (12.47 ± 0.40 ng/mL) compared with that without musical co-treatment (20.81 ± 1.16 ng/mL) and high-intensity exercise (26.91 ± 2.23 ng/mL). The plasma level of betatrophin was positively correlated with triglycerides ($r = 0.316$, $p \leq 0.05$), systolic blood pressure ($r = 0.428$, $p \leq 0.01$), HDL ($r = 0.366$, $p \leq 0.05$), energy expenditure ($r = 0.586$, $p \leq 0.001$), PGC-1 α ($r = 0.573$, $p \leq 0.001$), and irisin ($r = 0.863$, $p \leq 0.001$). By contrast, the plasma level of betatrophin was negatively associated with age ($r = -0.298$, $p \leq 0.05$) and LDL cholesterol ($r = -0.372$, $p \leq 0.05$). Importantly, betatrophin is a significant predictor for energy expenditure ($p \leq 0.001$) and plasma triglyceride levels ($p \leq 0.05$). **Conclusions.** Our data demonstrate that betatrophin levels decreased the post-MIE and musical therapeutical combination. Therefore, betatrophin may provide a benefit as the potential biomarker of physiological performance-associated physical training.

1. Introduction

Betatrophin is a potential lipid regulator that encompasses a relationship with the circulating level of triglycerides by inhibiting lipoprotein lipase [1, 2]. Betatrophin is strongly associated with metabolic syndrome risk factors, including dyslipidemia, hypertension, overweight, and obesity, impaired glucose tolerance, and development of T2DM [1, 3–8]. Similarly, betatrophin plays an essential role in the triglycerides control within circulation [9, 10]. On the other

hand, the silencing of betatrophin significantly decreases the circulating level of triglyceride [11, 12]. This liver hormone has the potential to regulate lipid metabolism and fatty liver incidence [1, 3, 5, 13]. The presence of a higher level of circulating betatrophin that was hypothesized was associated with the elevation of human triglycerides level even in the cell culture [14–16]. The alteration of circulating level betatrophin was predicted to result in precancer symptoms and enhance cancer development [17]. The higher level of betatrophin also reportedly occurred in T2DM participants

with kidney dysfunction (diabetic nephropathy) [18] and Indonesian ethnic with colorectal cancer [19]. Recently, it is portrayed that the endocrinal approach promises a significant future contribution against metabolic syndrome and its related diseases. Therefore, the pivotal role of betatrophin in controlling metabolic alteration may become a robust clinical biomarker for metabolic syndrome prevention.

Several previous investigations reported that hypertriglyceridemia significantly correlates with metabolic syndrome and diabetes [20–22]. The gradual increase of triglycerides levels was claimed as the essential inducer of metabolic syndrome, T2DM and its complication, and obesity [23–27]. Interestingly, the recent report shows that the higher incidence of obesity and diabetes is observed in Southeast Asian countries and more significant compared with that in other regions in the Asia Pacific [28]. Moreover, the manifestation of metabolic syndrome was reported higher to be in men than women [29] and correlated with eating behavior [30]. In addition, the incidence of metabolic syndrome was also found to increase along with age in particular postmenopausal stage of Asian population [31, 32]. Hence, this emerging health problem may offer an opportunity to be solved and prevent the development of the metabolic disorder in the population.

Nowadays, the administration of metabolic syndrome linked adiposity that can be managed by drugs, diet, and exercise therapy to improve the life span of individuals [33–36]. Combating metabolic disorder and its related disease is not only through a clinical approach but also may be supported by standardized exercise through intensive physical training. Exercises can modulate skeletal muscle metabolism, attenuate metabolic stress, and obesity, and re-establish the circadian cycle on the regular stage [37–39]. Fascinatingly, the co-treatment of the cinnamon extract with high-intensity exercise significantly alleviates metabolic syndrome [40]. Even though physical activities can be proposed as an alternative solution against metabolic syndrome, the discrepancies remain to exist. A previous study has shown that high-intensity exercise induces inflammation in female participants with metabolic syndrome [41]. Furthermore, this high-intensity exercise treatment in individual onset metabolic syndrome seems to corroborate metabolic perturbation in this subject [42]. Therefore, the invention of the novel preventive solution becomes essential to be conducted, and the potential therapy with high visibility and lower cost expense for metabolic syndrome in the global community is required.

During the last decades, several investigations have been conducted on how to cure metabolic syndrome and improve the metabolic rate without increased internal stressor activity within the human body. The recent finding presents that musical treatment can remove the stress, elevate the gastric and intestinal motility, reduce the cancer risk in the gastrointestinal tract, and increase the lipid metabolism [43]. The musical administration can enhance exercise endurance and reduce pain [44]. Nevertheless, the underlying impact of physical exercise and musical co-treatment in the individual on metabolic performance related to lipid metabolism hormone remains unclear. This study was conducted to

elucidate the correlation of musical-physical exercise co-interaction on the circulating level of betatrophin and metabolic profile in nonprofessional athletes.

2. Materials and Methods

2.1. Samples. Based on the ethical standards of the Declaration of Helsinki 1975, this study has been approved by the institutional review board (IRB), Faculty of Medicine, Universitas Brawijaya Malang, Indonesia, with the certificate of ethics number (106/EC/KEPK/04/2018). In the present study, the groups were divided into three categories, including high-intensity exercise, moderate-intensity exercise, and moderate-intensity with middle rhythm music co-treatment. The total number of participants involved in this study were 60 nonprofessional athletes with age criteria of 19–21 years old, body mass index of 19–23 kg/m², resting heart rate of 60–80 beats/minute, Hb levels of 13–15 g/dl, of blood pressure 120/100 mmHg, and level of physical fitness in both categories with VO₂ max (maximal oxygen volume) of 40–42 ml/kg/min which was verified by the Multi-level Multi-M Run Fitness Test. All participants were verified healthy both in terms of physical and psychological aspects. In general, the participants showed onset metabolic syndrome-related circulating triglyceride level. All participants had no illness or severe metabolic disorder and were administered by specific medical treatment. In addition, the participants were considered nonsmokers, nonalcoholic individuals, non-hypertensive, and nondiabetic family history. The participants were then invited to fill in the informed consent before the physical training program enactment.

2.2. Physical Exercise Treatment. The exercise program was applied and supervised by professionals at the sports center of the Faculty of Sports Science, Universitas Negeri Malang, Indonesia. The participants were then divided into three experimental groups consisting of high-intensity exercise with a heart rate of 80%–85% of maximum heart rate (HR_{max}), moderate-intensity exercise with a heart rate of 70%–75% of maximum heart rate, and moderate-intensity exercised combined with music. Prior to physical exercise enactment, the participants warmed up for five minutes with mild intensity exercise (heart rate of 40%–50% of HR_{max}). Further treatment was carried out by running on a treadmill for 30 minutes and done with data in each group. In this study, instrumental music was used (without song lyrics) with MP5 headphones during the running program. The music tempo used consisted of a moderate tempo with rhythms of 108–120 beats/minute and ≥80 dB (decibels).

2.3. Serological Analysis. The blood samples were taken after exercise training program by collecting 10 cc venous peripheral blood within vacutainer EDTA tubes, and plasma samples were then stored at –80°C. The plasma level of serological parameters were measured by the regular standardized protocol using a COBAS MIRA system. Furthermore, to measure the current level of betatrophin, a human

ELISA kit for lipasin or betatrophin was chosen (BT-lab science, China). The measurement of physical and anthropometric was determined, including age, weight, height, BMI, systolic blood pressure, and diastolic blood pressure.

2.4. Statistical Analysis. The normality test was performed to check data distribution by the Kolmogorov–Smirnov model. The comparison between all groups was made by using a parametric one-way ANOVA test, linear correlation with Pearson product-moment model, and univariate linear regression analysis with a 5% significant level. The results were shown as mean $\pm$ SE.

3. Results and Discussion

The general circulating biochemical parameters level of the participants involved in this study is shown in Table 1 and Figure 1. The participants' age, BMI, DBP, fasting blood glucose, HDL, LDL, and total cholesterol are not significantly different among the groups. The significant data were found in SBP and triglyceride levels. The systolic blood pressure (SBP) in moderate-intensity exercises combined with musical treatment is significantly lower than that in the high-intensity group. Similar results were observed in triglyceride levels ($p \leq 0.05$). The circulating triglyceride levels tend to decline in moderate-intensity exercise with musical co-treatment equal to the higher-intensity exercise model. Further analysis was addressed to obtain the basic profile of circulating level betatrophin in both different models of physical exercise. Importantly, the blood profile of betatrophin indicates that the plasma level of betatrophin significantly decreased in moderate-intensity exercise with musical co-treatment (Figure 2). Similar to the previous findings, the decrease of the betatrophin level simultaneously reduced the systolic blood pressure and triglyceride levels ($p \leq 0.05$) of the participants with musical-moderate-intensity exercise co-treatment. Based on our preliminary investigation, the significant association between betatrophin and some essential parameters for metabolic syndrome was found (Figure 3). The parametric analysis by Pearson product-moment linear correlation shows that the plasma level of betatrophin was significantly and positively correlated with the systolic blood pressure ($r = 0.428$, $p \leq 0.01$), HDL ($r = 0.366$, $p \leq 0.05$), triglycerides ($r = 0.316$, $p \leq 0.05$), energy expenditure ($r = 0.586$, $p \leq 0.001$), PGC-1 α ($r = 0.573$, $p \leq 0.001$), and irisin ($r = 0.863$, $p \leq 0.001$). Inversely, the plasma level of betatrophin was negatively associated with age ($r = -0.298$, $p \leq 0.05$) and LDL cholesterol ($r = -0.372$, $p \leq 0.05$). There was no significant correlation between betatrophin and other predictors, including BMI, diastolic blood pressure, fasting blood glucose, and total cholesterol (Table 2).

In the last stage of the data analysis, it was found that betatrophin has a correlation with metabolic rate, triglyceride level controlling, and muscle metabolism (Table 3). Importantly, betatrophin is a significant predictor for energy expenditure ($p \leq 0.001$), triglyceride levels ($p \leq 0.05$), plasma

levels of PGC-1 α ($p \leq 0.001$), and circulating irisin levels ($p \leq 0.001$). Furthermore, the type of relationship between betatrophin and these four response variables is a positive association (the parameter estimates are all positive), where the value of the responses will increase with the rise of betatrophin level and vice versa. Also, the significant test results for confounding variables in the regression model are shown in Table 4. Based on these data, it is found that betatrophin (X) is a significant predictor for triglyceride ($p \leq 0.001$). On the other hand, a group of exercise significantly affects either betatrophin ($p \leq 0.001$) or triglyceride ($p \leq 0.01$). It means that a group of exercises is a confounder. The presence of this confounder is in between the predictor (betatrophin) and the response (triglyceride). The exercise intervention can decrease the circulating level of betatrophin (negative value of parameter estimate = -7.080), while the level of triglyceride will increase as the rise of the betatrophin level (positive value of parameter estimate = $3,752$) (Table 4).

The results of this preliminary physical exercise intervention revealed that moderate-intensity exercise (MIE) treatment combined with musical middle rhythm beat was capable of contributing a positive effect on the circulating betatrophin level. Importantly, the results of this study generated a further hypothesis that the application of MIE treatment combined with musical middle rhythm beat to healthy nonprofessional athletes was able to decrease the circulating triglyceride in line with the decrease in the betatrophin expression. Betatrophin is a liver-derived hormone that is abundantly expressed in the liver and is the regulator of triglyceride in the circulation. The application of the physical treatment, especially the combination of moderate-intensity exercise and music, can stimulate a significant increase in energy expenditure. Furthermore, the application of this co-treatment linearly can increase the activity of muscle metabolism, whereas irisin and PGC-1 α expression significantly increased after the treatment (data not shown).

Betatrophin is a hormone that is generally produced in the liver and adipose tissue and clinically an essential regulator of triglyceride level and its metabolism [5, 6, 8, 9, 11]. Besides, the results of other research assert that betatrophin has a significant correlation with glucose metabolism [1, 4, 45], even though it failed to prove the role of this hormone in stimulated islet cell proliferation as the primary cell of insulin producer [46]. As one of the preventing model of metabolic syndrome, the application of exercise training, both short-term and long-term, was predicted to be able to influence an individual's physiological performance. Therefore, the administration of therapy and noninvasive models such as exercise was strongly perceived to become a potential prevention effort against metabolic syndrome development.

Significantly, this study reveals that the application of a moderate-intensity exercise model combined with music may contribute to the new theoretical model in preventing metabolic perturbation. Furthermore, intervention with short-time physical training programs can have a positive effect on metabolic parameters. Based on the data analysis, the application of physical exercise model combined with

TABLE 1: Biochemical characteristics of the study population from different groups.

Parameters	High intensity ($n = 20$)	Moderate intensity ($n = 20$)	Moderate intensity + music ($n = 20$)
Age (yrs)	20.07 $\pm$ 0.20	20.47 $\pm$ 0.19	20.73 $\pm$ 0.26
BMI (kg/m^2)	21.57 $\pm$ 0.39	21.85 $\pm$ 0.34	20.97 $\pm$ 0.27
SBP (mmHg)	145.33 $\pm$ 1.33	140.00 $\pm$ 1.69*	139.33 $\pm$ 1.53*
DBP (mmHg)	80.67 $\pm$ 2.06	80.66 $\pm$ 2.06	80.60 $\pm$ 1.07
Fasting glucose level (mg/dL)	73.07 $\pm$ 2.04	78.53 $\pm$ 2.73	72.27 $\pm$ 2.46
HDL (mg/dL)	58.33 $\pm$ 2.54	45.60 $\pm$ 2.40	48.53 $\pm$ 1.87
LDL (mg/dL)	88.33 $\pm$ 6.40	83.33 $\pm$ 4.65	89.87 $\pm$ 3.17
Total cholesterol (mg/dL)	165.87 $\pm$ 6.81	150.00 $\pm$ 4.76	166.33 $\pm$ 6.51
Triglyceride (mg/dL)	96.07 $\pm$ 8.71	105.47 $\pm$ 14.94*	99.20 $\pm$ 9.48
Betatrophin (ng/mL)	26.91 $\pm$ 2.23	20.81 $\pm$ 1.16*	12.47 $\pm$ 0.40*

SBP = systolic blood pressure, DBP = diastolic blood pressure; fasting glucose level, HDL, LDL, total cholesterol, triglyceride, and body temperature data were obtained from the postexercise program. One way-ANOVA, followed by Tukey's post hoc test, was used to compare the differences among groups. Data are presented as mean $\pm$ SE. *Significant value of each parameter compared with high-intensity exercise ($p \leq 0.05$).

FIGURE 1: Box-plot model for the differences between groups. (1) High-intensity exercise; (2) moderate-intensity exercise; and (3) moderate-intensity exercise + music. *Significant vs high-intensity exercise ($p \leq 0.05$).

music was able to lower the circulating betatrophin level, and lower triglyceride level equals to the group given high-intensity exercise. Besides being able to lower the triglyceride levels, the application of this co-treatment model can decrease the circulation stress-related blood pressure, where it is proven that there was a significant decrease in the systolic blood pressure. The same pattern was also observed in circulating level cortisol (data not shown). These data

implied that the potential development of this physical exercise model might be further set as a new approach for participants with metabolic disorders as an effort to prevent diseases related to metabolic disturbances.

Based on the previous investigations, it has been recommended that high-intensity interval training (HIIT) can increase more calories burning [47]. Exercise will increase "being" subcutaneous white adipose tissue and stimulate

FIGURE 2: The circulating levels of betatrophin after MIE with musical co-treatment. *Significant vs high-intensity exercise ($p \leq 0.05$).

fatty acid oxidation [48]. Moderate-intensity physical training established is recommended to be applied as an essential model to enhance lipid oxidation within the mitochondria [49]. Even though loud music was able to enhance the optimal performance of physical exercise during treadmill administration at a younger age [50], the high-intensity exercise combined with fast music results in a higher level of stress hormone (cortisol) and induces catabolism in skeletal muscle. Music has a different impact on metabolic performance, depending on the training level [43]. The possible mechanism on how music results in the increase of metabolic performance was hypothesized related to the HPA (hypothalamic-pituitary-adrenal) axis [43]. The physiological stress caused by high-intensity physical training will trigger the sympathetic nervous system (SNS) to enhance the adrenalin effect on vascular tension. However, the music application can decrease the stress hormone (cortisol) and reduce the heart rate and cardiac output [51]. Music can increase the body endurance and elevated oxygen uptake [52] while lowering the respiration rate through inducing the parasympathetic pathway [53]. The musical exposure during low-intensity physical exercise can trigger better performance for endurance equal to high-intensity training [54]. Another study has shown that video-game music was able to decrease proinflammatory cytokine, serum adipokine, and lipid levels after one-month training [55]. In accordance with our findings, the physical training with moderate-intensity exercise combined with music decreases the circulating level of stress hormone and proinflammatory cytokine $\text{TNF-}\alpha$ and interleukin-6 (IL-6) levels (data not shown). The better performance of metabolic rate-related energy expenditure showed to be more significant in moderate-intensity exercise co-treated with music. We speculate that this exercise model may enhance the fatty acid oxidation and lower the circulating level of triglycerides supported by the significant gradual changes of plasma level

of betatrophin and increase the lipoprotein lipase activity in the peripheral. The combination model was acting through the HPA axis to reduce the vascular pressure without any significant negative impact on the individual metabolic performance. In addition, we suggest that the long-term MIE-musical treatment be used to enhance the thermogenesis-related adipose tissue and enhance browning in this site. However, a further expanded trial is required to improve our hypothesis.

Also, in line with our data, the results of the previous clinical test stated that the application of the exercise training therapy model in the long-term approach (3-month treatment) on individuals with obesity was able to lower the triglyceride levels corresponding to the gradual decreased circulating level betatrophin [56]. Furthermore, the results of another study in an animal model and human trial proved that exercise could lower liver steatosis and improve fatty acid oxidation [57], lower excess deposit fatty acid and glucose in peripheral tissue [58], and lower hepatic fat content in an individual with prediabetic symptoms [59]. The long-term model for physical exercise (8 weeks to 6 months) significantly reduces the lipid concentration within the liver through increased lipid oxidation [60]. Interestingly, by contrast, it was claimed that the acute exercise model for four hours of treatment could not decrease the fat within the liver in male participants with a nonalcoholic fatty liver [59, 61]. The discrepancy among several previous studies may be due to the variation of a treatment model for physical exercise and also the different subjects or participants that have been chosen. Thus, the exploration of a novel model for combating metabolic syndrome using exercise training may urgently be required.

Several recommendations from the clinical trial have proved that exercise is a potential model against metabolic syndrome related to obesity and insulin resistance-linked diabetes by changing the lifestyle through increased physical

FIGURE 3: Univariate correlations with plasma betatrophin. The significant linear correlation between parameters was visualized in the plot model ($p \leq 0.05$).

exercise [62–64]. In this study, this is the first-time model by combining a short-term moderate-intensity exercise with musical co-treatment. Importantly, the data of this study indicate that MIE with musical combination may be able to be the future prevention approach for metabolic syndrome by lowering the gradual increase in its risk factor, including liver-derived hormone, betatrophin, or lipasin that regulate the circulating triglyceride level. Also, MIE and music can decrease other risk factors for metabolic syndrome, for instance, blood pressure and triglycerides. Collectively, these data support the notion that MIE and betatrophin can be exploited as the potential target and future candidate for combating metabolic syndrome-associated obesity and

other health problems-linked lipid metabolism. Even though this study contributes to the development of the metabolic syndrome prevention model, our study is open to some limitations. First, in this study, we cannot provide comprehensive data for the whole part of the physiological indicators or parameters of the participants. Second, the exercise model only compared the plasma level of betatrophin and another biochemical parameter with high- and moderate-intensity exercise treatment of participants' onset metabolic syndrome. Accordingly, future works are encouraged to focus on the long-term treatment of MIE and musical co-treatment to the expression of betatrophin in an individual with the metabolic syndrome medical record. The

TABLE 2: Univariate correlations with plasma betatrophin in all participants.

Parameters	Betatrophin	
	<i>r</i>	<i>p</i> value
Age (yrs)	−0.298*	0.047
BMI (kg/m ²)	0.089	0.563
SBP (mmHg)	0.428*	0.003
DBP (mmHg)	0.013	0.932
Fasting glucose level (mg/dL)	0.062	0.688
HDL (mg/dL)	0.366*	0.014
LDL (mg/dL)	−0.372*	0.012
Total cholesterol (mg/dL)	−0.061	0.689
Triglyceride (mg/dL)	0.316*	0.034
Energy expenditure (Cal)	0.586*	<i>p</i> ≤ 0.001
Irisin (ng/mL)	0.863*	<i>p</i> ≤ 0.001
PGC-1α (ng/mL)	0.573*	<i>p</i> ≤ 0.001

*Significant with *p* ≤ 0.05 by Pearson's product-moment correlation test.

TABLE 3: Univariate linear regression analysis.

Response	Predictor	Estimate	<i>p</i> value
Energy expenditure	Betatrophin	2.250	<i>p</i> ≤ 0.001*
Triglyceride	Betatrophin	1.688	0.034*
Irisin	Betatrophin	0.370	<i>p</i> ≤ 0.001*
PGC-1α	Betatrophin	0.064	<i>p</i> ≤ 0.001*

*Significant with *p* ≤ 0.05.

TABLE 4: Test for confounding effect using univariate and multivariate regression analysis.

Response	Predictor	Estimate	<i>p</i> value
Triglyceride	Betatrophin	3.752	0.001*
	Group of exercise	28.129	0.008*
Betatrophin	Group of exercise	−7.080	<i>p</i> ≤ 0.001*

*Significant with *p* ≤ 0.05.

serological analysis must be addressed to all supporting parameters that are potentially involved in the pathogenesis of the metabolic syndrome. This model may also be applied to an individual with hypertriglyceridemia developed to obesity in the younger and elder ages to obtain a better understanding of the essential role of this exercise model in several cases related to metabolic diseases.

4. Conclusion

In general, our investigation shows that acute moderate-intensity exercise and the musical combination model decreased the plasma level of betatrophin. MIE co-treated with music can reduce the circulating level of triglyceride and vascular tension linear to the gradual decrease of betatrophin. Hence, physical exercise and harmonious co-treatment may regulate betatrophin and triglyceride homeostasis.

Abbreviations

MIE: Moderate-intensity exercise
ELISA: Enzyme-linked immunosorbent assay

HDL: High-density lipoprotein
LDL: Low-density lipoprotein
PGC-1α: Peroxisome proliferator-activated receptor gamma co-activator 1 alpha
BMI: Body mass index
T2DM: Type 2 diabetes mellitus
SBP: Systolic blood pressure
DBP: Diastolic blood pressure.

Data Availability

All the datasets generated in the current study are available from the corresponding author upon a reasonable request.

Ethical Approval

This experimental study was conducted according to the Declaration of Helsinki and approved by the institutional review board (IRB), Faculty of Medicine, Universitas Brauwijaya Malang, Indonesia, with the certificate of ethics number 106/EC/KEPK/04/2018.

Consent

The participants filled the informed consent and agreed to moderate-intensity data within this article.

Conflicts of Interest

The authors declare that there are no conflicts of interest in this work.

Authors' Contributions

Hendra Susanto conceived the research and contributed to the research project design, data analysis, data interpretation, and writing of the manuscript. Ahmad Taufiq contributed to the data analysis, data interpretation, and writing of the paper. Sugiharto, Desiana Merawati, Khumaira Marsyidah Badu, and Adeodatus Yuda Handaya contributed to research project design and data collection. Jerry Dwi Trijoyo Purnomo contributed to the statistical analysis and writing of the manuscript.

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