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by Sugiharto Sugiharto

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RESEARCH ARTICLE

Acute Interval and Continuous Moderate-Intensity Exercise Enhanced Circadian Thermogenic Activity through Browning-related Genes in Obese Adolescent Female

Sugiharto[a,*], Desiana Merawati[a], Adi Pranoto[b], Purwo Sri Rejeki[c], Moch. Nasmay Lupita[a], Banih Sakti Adji[a], Hendra Susanto[d], Ahmad Taufiq[e]

[a] Department of Sports Science, Faculty of Sports Science, Universitas Negeri Malang, Malang, Indonesia; [b] Medical Science, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia; [c] Department of Physiology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia; [d] Department of Biology, Faculty of Mathematics and Natural Sciences, Universitas Negeri Malang, Malang, Indonesia; [e] Department of Physics, Faculty of Mathematics and Natural Sciences, Universitas Negeri Malang, Malang, Indonesia.

Abstract Thermogenesis is associated with oxidation activity in muscle and fat tissue, the target of non-pharmacological therapy in preventing the increase in obesity. This research was designed to reveal the circadian profile of thermogenic gene expression after the acute interval and continuous moderate-intensity exercise. The subjects were 22 randomly selected obese adolescent females who met the predetermined inclusion criteria. The study subjects were then divided into three groups: control group (CG), acute interval moderate-intensity exercise group (AIMIE), and acute continuous moderate-intensity exercise group (ACMIE). Acute interval and continuous exercise were performed by running on a treadmill for 40-45 minutes, while moderate-intensity was defined as 60%-70% of the maximum heart rate (HRmax). The blood samples were collected initially (pre-exercise), followed by 10 minutes, 6 hours, and 24 hours post-acute interval and continuous moderate-intensity exercise treatment. Measurement of peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PGC-1α) and fibronectin type III domain 5 (FNDC-5) expressions in protein level were confirmed by enzyme-linked immunosorbent assay (ELISA) method. Data were analyzed using one way-ANOVA and two way-ANOVA with a significant level of 5%. The findings suggest a substantial increase in the expression of PGC-1α and FNDC-5 after exercise compared to before the workout. A significant difference in PGC-1α and FNDC-5 expressions between the control group compared to AIMIE and ACMIE ($p \leq 0.05$) has been observed. However, there is no significant difference in PGC-1α and FNDC-5 expressions after exercise between AIMIE and ACMIE ($p \geq 0.05$). In conclusion, acute interval and continuous moderate-intensity exercise increase the expression of thermogenesis-related genes. Hence, acute interval and continuous moderate-intensity exercise might be potential non-pharmacological therapy to prevent, reduce, and control the increasing prevalence of obesity.

Keywords: Thermogenic, exercise, PGC-1α, FNDC-5, obesity

***For correspondence:**
sugiharto@um.ac.id

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Introduction

Obesity has been classified as a global disease [1] that severely impacts human health [2]. Obesity is a disease that has caused a high risk of complications [3], disability [4] and premature death [5], and

morbidity and mortality in the global community [6]. This is because obesity can lead to an increased risk of cardiovascular disease [7], type 2 diabetes [8], mitochondrial dysfunction [9], metabolic disorders [10], and several types of cancer [6]. Previous studies recommend that obesity prevention and control can be carried out using approaches, such as eating behavior transformation [11], reducing calorie intake diet, giving nutritional supplements consumption [6], lifestyle modification [12], changing environmental conditions [1], and also a pharmacological approach by providing drugs [13]. However, some of the methods recommended by previous studies are still considered ineffective [1] because they increase risk factors for complications and cause dependence [6], and require significant costs [2]. This approach is considered effective in the short term [8] because it can only reduce lean body weight, lower basal metabolism, and increase the risk of nutritional deficiencies [11]. Therefore, a non-pharmacological approach based on exercise is required. Exercise carries physiological effects that significantly affect the body [13], one of which it increases the expression of the thermogenesis gene [14] and activates the adipose network, decreasing lipid accumulation [15]. Therefore, the preparation of an exercise program as a non-pharmacological therapy for obese individuals through increasing activity of thermogenic genes is interesting to be developed further [16].

Exercise increases muscle contraction, a contributor to thermogenesis induced by the activation of the uncoupling protein-1 (UCP-1) thermogenic gene [17]. Exercise increases the need for adenosine triphosphate (ATP), which will change the AMP/ATP ratio [18]. The change in the AMP/ATP ratio stimulates an increase in peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PGC-1α) [19] and fibronectin type III domain-containing protein 5 (FNDC-5), transformed into irisin molecules and is often found in circulation [20]. Increased irisin activates UCP-1 [21], causing white adipose tissue browning activity (WAT) [22]. Meanwhile, the browning in WAT triggers thermogenesis activity [9] via extracellular-signal-regulated kinase (ERKs) and p38 mitogen-activated protein kinase (p38-MAPK) pathways [23] and activation of lipolysis [24]. The increase in lipolysis causes the breakdown of triglycerides as an increased energy source [25], increases energy expenditure via oxidative phosphorylation [14], regulates glucose and lipid homeostasis [20], which affects the metabolic health [11]. Thus, thermogenesis is an attractive potential non-pharmacological therapy target for obesity prevention and management [24].

Exercise provides opportunities as a form of non-pharmacological therapeutic approach capable of involving integrative and adaptive responses at the tissue, organ, cellular, molecular, and system levels simultaneously [26]. Furthermore, exercise intensity has an essential role in response and adaptation [27], which affects the expression of thermogenic genes [28]. The results of previous in vivo animal models concluded that high-intensity exercise increased transformation to thermogenic genes faster than moderate-intensity exercise [29]. Inversely, other studies have concluded that moderate-intensity exercise is more beneficial than a high-intensity exercise in increasing response and adaptation to the browning gene and cause no systemic injury to muscles [15]. High-intensity exercise increases the browning gene adaptation faster, but it carries a higher risk of inflammation and systemic injury [17]. In addition, high-intensity exercise can also increase stressors and disrupt homeostasis [30] and triggers tissue damage [31]. Hence, moderate-intensity exercise is a safe exercise for obesity prevention and its complications [11]. Besides, it also follows the level of physical fitness of the general public, especially subjects with obesity [32].

Increased thermogenesis in exercise is an important marker that links metabolic regulation with targeted therapy to prevent and treat metabolic syndrome and obesity [33]. After exercise, therapeutic gene expression has been observed as a healing target in preventing and treating overweightness, globally. In addition, exercise is predicted to be an effective and strategic method for improving metabolic health [34] and improve metabolic profiles [35]. Although previous studies claim that exercise can enhance the performance of thermogenic gene expression related to metabolism [15, 29], but the effect of acute interval training and continuous moderate-intensity exercise on changing the thermogenesis profile of circadian genes in obese individuals has not been investigated, further. Therefore, this study seeks to uncover changes in the circadian profile of thermogenic gene expression after the acute interval and continuous moderate-intensity exercise. The acute interval and continuous moderate-intensity exercise are synthesized to enhance the circadian profile of thermogenic gene expression in obese individuals.

Materials and Methods

Experimental Design and Exercise Treatment

Based on the ethical standards of the Declaration of Helsinki 1975, this research procedure has received approval from the Health Research Ethics Commission (IRB) Faculty of Medicine, University of Brawijaya Malang (number 26/EC/KEPK-S1/02/2020). In this study, a truly experimental approach with a Basic Time Series Design using adolescent females was employed. The inclusion criteria for the subjects were

obese adolescent females with body mass index of 27-35 kg/m^2, age of 18-22 years, percentage of body fat > 30%, normal blood pressure, resting heart rate (60-80 bpm), fasting blood glucose < 100 mg/dL, normal hemoglobin, excellent category of VO_2max and classified as healthy based on a doctor's examination. All subjects had received information directly and in writing about the objectives, procedures, rights, and obligations in this study. Twenty-two prospective subjects met the inclusion criteria and stated their willingness to become research subjects. Then, the research subjects were divided randomly into three groups: control group (CG), acute interval moderate-intensity exercise group (AIMIE), and acute continuous moderate-intensity exercise group (ACMIE). The subjects were fasted for 8 hours starting at 10.00 p.m. before the exercise treatment on the next day.

The exercise intervention was given to the research subjects at 6.30–10.30 a.m. [36], which begins with a medical examination and blood sampling before exercise (pretest) PGC-1α, FNDC-5, and UCP-1 examinations. After taking blood samples (before exercise), the subject was given a drink containing 5% glucose levels [37], then the subjects took a rest for 30 minutes [38]. After 30 minutes of resting, the subject was given an exercise intervention. The exercise was carried out in the Fitness Center of the Health Ministry of Malang with room temperature between 22–25 °C [39] with a humidity level of 50-70% [40]. Exercise interventions were completed using a treadmill (Richter Treadmill Semi-Commercial Evolution (4.0 HP DC); Richter Fitness, Taipei, Taiwan) with inclination levels of 0% [38]. It was carried out by running on a treadmill at intervals for group 2 (AIMIE) and continuously for group 3 (ACMIE) with moderate intensity. Before the core workout, a 5-minutes warm-up and 5 minutes cool-down after the core workout with low-intensity were completed. Meanwhile, the AIMIE group exercised for 45 minutes, consisting of running 5 minutes, followed by a rest period of 2.5 minutes (ratio of work to rest 1:1/2), repeated five times. The rest was carried out using active rest by running low-intensity [41], while ACMIE did a continuous exercise of moderate-intensity for 40 minutes continuously (without rest). The moderate intensity and light intensity were equal to 60%–70% and 50%–60% of HRmax, respectively [42]. Intensity measurement was carried out using a measurement formulation of HRmax: HRmax – age in years (220 – age in years) [39]. The heart rate was monitored during exercise using a polar heart rate monitor (Polar H 10 Heart Rate Sensor, USA. Inc).

Baseline Data Collection

Anthropometric measurements of height used was a stadiometer (SECA, Chino, CA) while measuring body weight, body mass index, percentage of body fat, Fat Mass, Free Fat Mass, Muscle Mass, and Basal Metabolic Rate, were carried out using TANITA (Body Composition Analyzer DC3607601 (2) - 1604 FA, TANITA Corporation of America, Inc). Furthermore, pressure measurements used an automated device (OMRON Model HEM-7130 L, Omron Co., JAPAN) and for heart rate measurement using Polar (Polar H10 Heart Rate Sensor, USA, Inc). Measuring VO_2max was completed using the Astrand-method with an ergo cycle device (Monark 828 E, Version 1010 Art. No: 7950-296, Vansbro, Sweden). Blood samples were collected four times for expression examination of PGC-1α, FNDC5, and UCP-1, before exercise, 10 minutes after exercise, 6 hours after exercise, and 24 after exercise. After the second blood sample was taken (10 minutes after the exercise), the subjects were given fruit prayer consumption, food, drink and brought back to the guest house for rest and preparation for the third and fourth blood sampling. The subjects were fasted again for 2 hours before blood sampling for the third and fourth blood sampling. Meanwhile, the control group did not do any exercise but get the same procedure for blood sampling as the intervention group (AIMIE and ACMIE).

Serological Assay

Blood samples were taken from 5 ml cubital veins [43]. The blood that had been drawn was put into a 6 ml vacutainer, then centrifuged for 15 minutes at 3000 rpm speed. Serum was separated and stored at -80 °C for level analysis of PGC-1α, FNDC5, and UCP-1 in the Physiology Laboratory Faculty of Medicine Universitas Brawijaya Malang. Measurement of PGC-1α levels was completed using an ELISA kit (Catalog No. E-EL-H1359; Elabscience, Inc., China, 2020) with a sensitivity level of PGC-1α in the kit 0.10 ng/mL. Measurement of FNDC5 levels used an ELISA kit (Catalog No. E-EL-H2254; Elabscience, Inc., China, 2020) with a sensitivity level of FNDC-5 in the kit 0.1 ng mL. Meanwhile, the UCP levels -1 was measured by the ELISA method (Catalog No. E-EL-H1661; Elabscience, Inc., China, 2020) with UCP-1 sensitivity level in the 0.10 ng/mL kit. The sandwich and competitive ELISA method was used as a measurement method. Measurement of Fasting Blood Glucose used ACCU-CHEK (ACCU-CHEK® Performance, Mannheim, Germany) with mg/dL concentration units. Measurement of Hb using Easy Touch (Easy Touch GCHb, Taiwan) was carried out with a g/dL concentration unit.

Data Analysis

The normality test was completed using the Shapiro-Wilk test, followed by the homogeneity test using the Levene test. Different tests using one-way-ANOVA, two-way-ANOVA and followed by Tukey's Honestly Significant Difference (HSD) post hoc test and Pearson product-moment correlation test were used to determine the relationship between PGC-1α and anthropometrics and biomarkers of

thermogenesis. All data are presented as mean ± Standard Deviation (SD). All statistical analyzes used a significant level ($p \leq 0.05$).

Results and Discussion

The one Way-ANOVA Test results suggest no significant difference in the characteristics between the control group, the acute interval moderate-intensity exercise group, and the acute continuous moderate-intensity exercise group ($p \geq 0.05$) (**see Table 1, Figure 1, and Figure 2**). Furthermore, no significant difference in the expression of the thermogenic genes PGC-1α, FNDC-5, and UCP-1 baseline (before exercise) between CG, AIMIE, and ACMIE ($p \geq 0.05$) (**Table 2**) has been observed. Importantly, the UCP-1 thermogenic gene expression at 10 minutes, 6 hours, and 24 hours after exercise is concluded based on the significant difference between CG, AIMIE, and ACMIE ($p \leq 0.05$). Further analysis of UCP-1 thermogenic gene expression at 10 minutes following the exercise based on Tukey's HSD post hoc test results showed a significant difference between AIMIE and CG ($p \leq 0.001$), along with ACMIE and CG ($p \leq 0.001$). Simultaneously, there is no significant difference between AIMIE and ACMIE ($p \geq 0.05$). The UCP-1 gene expression tested 6 hours after exercise of the control group is significantly different from the AIMIE and ACMIE groups ($p \leq 0.001$). Meanwhile, no significant difference between AIMIE and ACMIE ($p \geq 0.05$) has been observed. Similar results were also found in the measurement of UCP-1 expression at 24 hours post-exercise (**Figure 3**).

Table 1. Characteristics of the Research Subjects

Variable	Group			One Way-ANOVA
	CG (*n*=7)	AIMIE (*n*=7)	ACMIE (*n*=8)	*p-values*
Age (years)	19.71±1.49	19.57±1.51	20.00±1.52	0.854
Body Weight (kg)	72.99±5.71	73.58±8.34	74.47±7.45	0.923
Body Height (m)	1.57±0.04	1.58±0.06	1.58±0.05	0.963
BMI (kg/m^2)	29.21±1.03	29.11±1.55	29.74±1.62	0.666
SBP (mmHg)	114.71±2.87	114.43±2.82	114.62±2.45	0.980
DBP (mmHg)	77.43±3.78	76.29±3.49	77.88±3.72	0.699
RHR (bpm)	73.86±8.69	70.57±8.10	74.50±4.24	0.544
VO_{2max} (mL/kg/min)	28.61±3.81	26.23±1.14	27.31±1.22	0.193
FBG (mg/dL)	92.43±5.09	92.42±3.31	87.87±5.46	0.124
Hb (g/dL)	15.74±1.82	15.39±0.88	14.25±1.03	0.090
PBF (%)	45.71±3.83	43.91±2.24	44.02±4.05	0.563
FM (kg)	34.53±6.41	32.46±4.52	33.00±5.71	0.775
FFM (kg)	40.63±4.10	41.31±4.61	41.52±2.99	0.901
MM (kg)	38.24±3.76	38.86±4.23	39.05±2.73	0.905
BMR (kcal)	1361.00±142.23	1366.43±151.35	1380.12±97.29	0.958
Waist (cm)	93.29±13.88	85.57±8.79	88.37±7.99	0.392
Hip (cm)	108.14±4.29	108.00±6.73	108.50±5.42	0.984
WHR	0.82±0.03	0.79±0.05	0.81±0.04	0.305

Description: BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; RHR: Resting Heart Rate; FBG: Fasting Blood Glucose; PBF: Percentage Body Fat; FM: Fat Mass; FFM: Free Fat Mass; MM: Muscle Mass; BMR: Basal Metabolic Rate; WHR: Waist to Hip Ratio; VO_{2max}: Volume Oxygen Maximum; CG:Control Group; AIMIE: acute interval moderate-intensity exercise; ACMIE: acute continuous moderate-intensity exercise. All data are presented with Mean±SD.

The results of serological testing for other thermogenic gene expression PGC-1α at 6 hours and 24 hours after exercise showed no significant difference between CG, AIMIE, and ACMIE ($p \geq 0.05$) (**Table 2**). However, the expression of the thermogenic PGC-1α gene at 10 minutes after exercise showed significantly different results among the three groups ($p \leq 0.05$). Besides, the results of the further analysis with Tukey's HSD post hoc test showed a significant difference between ACMIE and CG ($p \leq 0.05$), no significant difference between AIMIE and CG ($p \leq 0.05$), along with no substantial difference between AIMIE and ACMIE ($p \geq 0.05$) (**Figure 4**). Interestingly, the thermogenic FNDC-5 gene expression analysis at 10 minutes, 6 hours, and 24 hours after exercise also presents a significant distinction between CG, AIMIE, and ACMIE of ($p \leq 0.05$) (**Table 2**). The results of Tukey's HSD post hoc test of thermogenic gene expression FNDC5 at 10 minutes after exercise demonstrated a significant

difference between AIMIE and CG of ($p \leq 0.05$), ACMIE, and CG of ($p \leq 0.05$). However, no substantial difference between ACMIE and AIMIE ($p \geq 0.05$) has been observed from that test results. Moreover, the expression of the thermogenic gene FNDC5 at 6 hours after exercise also presents a meaningful difference between AIMIE and CG ($p \leq 0.05$), as well as between ACMIE and CG ($p \leq 0.05$). However, there is no significant difference between ACMIE and AIMIE ($p \leq 0.05$). Expression testing at 24 hours post-exercise showed a significant difference between ACMIE of and CG of ($p \leq 0.05$), but no significant difference between AIMIE and CG ($p \leq 0.05$) and ACMIE and AIMIE ($p \geq 0.05$) (**Figure 5**). In the relationship analysis with the Pearson Product Moment correlation test, a significant relationship between PGC-1α and body weight ($r = –0.564$, $p \leq 0.001$), BMI ($r = –0.705$, $p \geq 0.05$), PBF ($r = –0.506$, $p \geq 0.05$), and FM ($r = –0.617$, $p \leq 0.001$). PGC-1α expression was also closely related to irisin ($r = 0.759$, $p \leq 0.001$), UCP-1 ($r = 0.718$, $p \leq 0.001$), betatrophin ($r = –0.659$, $p \leq 0.001$), MDA ($r = –0.796$, $p \leq 0.001$) and cortisol ($r = –0.538$, $p \leq 0.001$) have been identified (**Table 3 and Figure 6**).

Table 2. Analysis Results of PGC-1α, FNDC-5, and UCP-1 Levels

Variable	Duration	Group			One Way-ANOVA
		CG (*n*=7)	AIMIE (*n*=7)	ACMIE (*n*=8)	*p-values*
PGC-1α (ng/mL)	Baseline	2.31±1.55	2.23±1.99	2.25±0.56	0.994
	10 min post-exercise	2.06±1.26	3.57±0.89*	3.95±1.68*	$p \leq 0.05$
	6 hr post-exercise	2.32±1.49	3.28±1.76	3.02±0.79	0.420
	24 hr post-exercise	2.27±1.01	2.94±1.79	2.62±0.93	0.629
FNDC-5 (ng/mL)	Baseline	10.84±3.13	10.67±3.99	10.66±1.86	0.992
	10 min post-exercise	10.48±3.25	13.67±0.95*	14.21±0.77*	$p \leq 0.05$
	6 hr post-exercise	10.58±3.41	13.55±1.06*	13.88±0.43*	$p \leq 0.05$
	24 hr post-exercise	10.38±3.71	13.26±0.69	13.63±0.57*	$p \leq 0.05$
UCP-1 (ng/mL)	Baseline	3.67±0.42	3.60±1.28	3.91±1.39	0.862
	10 min post-exercise	3.71±0.63	5.57±0.40*	6.39±0.96*	$p \leq 0.001$
	6 hr post-exercise	3.69±0.77	5.21±0.51*	5.51±0.38*	$p \leq 0.001$
	24 hr post-exercise	3.70±0.33	4.95±0.52*	5.12±0.59*	$p \leq 0.001$

*Significant vs. control group (CG) ($p \leq 0.05$). All data are presented with Mean±SD.

In general, the results suggest a significant difference in the expression of thermogenic genes in individual circadian cycles within obese subjects between both acute interval moderate-intensity exercise and acute continuous moderate-intensity exercise compared to the control group. The difference in the expression of the activity of thermogenic genes is strongly presumed to be an effect of the intervention because the characteristics of the subjects are associated with changes in the circadian cycle of thermogenic gene activity, such as UCP-1 and PGC-1α [44]. Substantially, obese subjects are susceptible to specific exercises compared to normal weight subjects [7]. Obese individuals can carry out moderate-intensity exercise because they tend to have low muscle mass [45], high fat mass, and easy fatigue [30], while high-intensity exercise should be avoided [16]. Physiologically and psychologically, moderate-intensity exercise is very suitable, comfortable, and enjoyable for obese subjects [7], so based on our hypothesis, moderate-intensity exercise will significantly affect changes in the circadian cycle of thermogenic genes in the subjects of this study.

Based on the analysis results in the moderate-intensity interval and continuous exercise, the changes in the circadian cycle of the UCP-1 thermogenic gene at 10 minutes, 6 hours, and 24 hours post-intervention are different with the control group. It is in line with the results of previous studies that the increased expression of the UCP-1 thermogenic gene in obese non-diabetic adults after giving 70%-80% intensity exercise [46]. In their study, Tanaka et al. [15] also concluded an increase in UCP-1 expression in adult men with average body mass index after moderate-intensity walking exercise [15]. Research using experimental animals with weight exercise also concluded that exercise increases the UCP-1 thermogenic gene [47], activity of thermogenic genes such as PGC-1α, UCP-1, as well as acid transport genes after moderate-intensity continuous exercise and high-intensity interval exercise [29]. The increase in the UCP-1 thermogenic gene is not only observed in regular exercise but also in acute exercise [20]. This increase is the effect of increased PGC-1α expression caused by muscle contraction during exercise [48], which in turn increases FNDC5-induced irisin release [49]. Meanwhile, the increased irisin release enhances the activation of the UCP-1 gene [20], causes an increase in browning activity which accelerates the thermogenetic activity [9]. In addition, moderate-intensity acute exercise is a myokine stimulant [18], which will carry changes in the circadian cycle of thermogenic genes [50].

Interestingly, in our study with UCP-1 examination at 6 hours and 24 hours after exercise, the circadian cycle of the UCP-1 gene is lower compared to UCP-1 levels at 10 minutes after exercise. However, the decrease in UCP-1 levels at 6- and 24-hours post-workout remains higher than that of placebo. In line with our findings, Kim et al. stated that UCP-1 levels decrease at 12 hours post [51]. It is hypothesized that the increase of UCP-1 posts 10-minute moderate-intensity exercise strongly correlates to the irisin level. Also, previous study has mentioned that irisin expression grows highest 1 hour after exercise and decreases significantly 6 hours after exercise [52], while the increasing expression of the thermogenic UCP-1 gene activates irisin [20]. As the result, decreased irisin expression affects the UCP-1 thermogenic gene activity [53]. Interestingly, our results suggest that the UCP-1 circadian cycle changes have the same pattern as the PGC-1α and FNDC-5 gene changes cycles (Figure 4-5), so that elevation of UCP-1 can be a potential for obesity exercise therapy [20].

Table 3. Linear Correlation Analysis between PGC-1α and Subjects' Characteristics

Parameter	PGC-1α	
	r	*p-values*
Age (years)	0.362	0.090
Weight (kg)	–0.564*	p ≤ 0.001
Height (m)	–0.261	0.228
BMI (kg/m^2)	–0.705*	p ≤ 0.001
SBP (mmHg)	–0.385	0.069
DBP (mmHg)	–0.180	0.412
RHR (bpm)	–0.354	0.097
VO_2max (mL/kg/min)	0.226	0.301
FBG (mg/dL)	–0.439*	0.036
PBF (%)	–0.506*	0.014
FM (kg)	–0.617*	p ≤ 0.001
FFM (kg)	–0.379	0.075
MM (kg)	–0.449*	0.032
BMR (kcal)	–0.557	0.128
Waist (cm)	–0.362	0.090
Hip (cm)	–0.342	0.111
WHR	–0.209	0.338
Irisin (ng/mL)	0.750*	p ≤ 0.001
UCP-1 (ng/mL)	0.718*	p ≤ 0.001
IGF-1 (ng/mL)	0.743*	p ≤ 0.001
Betatrophin (pg/mL)	–0.659*	p ≤ 0.001
MDA (ng/mL)	–0.796*	p ≤ 0.001
Cortisol (ng/mL)	–0.538*	p ≤ 0.001

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

Based on the analysis results of moderate-intensity exercise, both interval and continuous exercise increase the circadian cycle changes of the thermogenic genes PGC-1α and FNDC-5 at 10 minutes, 6 hours, and 24 hours after exercise, compared to the control group. The increase in PGC-1α after exercise stimulates a growth in FNDC-5 protein, which cleavages to form irisin [54], activating the UCP-1 thermogenic gene to enhance thermogenesis [14]. Previous studies also reported higher PGC-1α in experimental mice after swimming treatment than in the control group [55]. The same results have been reported on the mouse model after 30 minutes of treadmill exercise [53]. Lee et al. [56], in their research, also concluded that moderate-intensity workout (60%-70% VO_2max) increases PGC-1α expression [56]. The results of other studies also claim that 45 minutes of exercise with 70% VO_2max intensity increases PGC-1α gene expression in individual circadian cycles. That peak PGC-1α gene expression is estimated to occur 2 hours after exercise [57]. Several other studies also reported that administering moderate-intensity, high-intensity, and exercise at the anaerobic threshold of peak PGC-1α gene expression occurred 3 hours after exercise [58]. The peak is observed between 2-3 hours [59], while in experimental animals, it is estimated 3 hours after exercise [48]. Furthermore, the decreasing trend of PGC-1α in the mouse model occurred 6 hours after 30 minutes of treadmill exercise [53]. Changes in the circadian cycle of the PGC-1α thermogenic gene are closely related to irisin [60] in triggering browning [28]. Meanwhile, moderate-intensity exercise has a better response to the circadian cycle change of thermogenic gene

expression than high intensity or anaerobic threshold [58]. The increase in the PGC-1α thermogenic gene in moderate-intensity exercise is extremely substantial as it modulates various metabolic processes, increases mitochondrial biogenesis, increases browning and thermogenesis so that it becomes a potential therapeutic target [61]. Hence, moderate-intensity exercise is expected to attract public interest to addopt a healthy and active lifestyle for non-pharmacological therapy, especially in obese subjects.

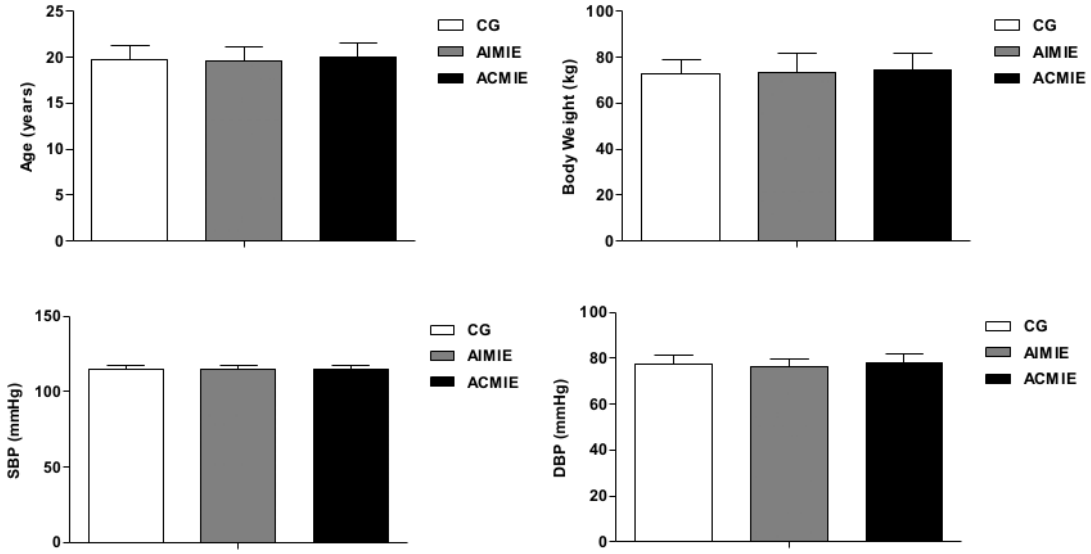


Figure 1. Bodyweight, age, blood pressures (systole and diastole) between the research subject groups

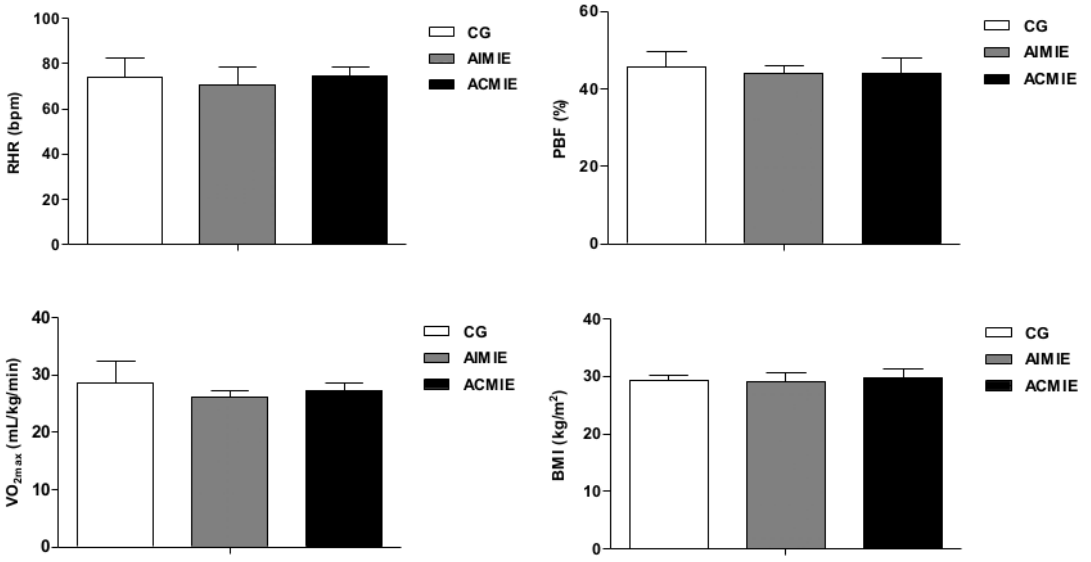


Figure 2. RHR, FBF, VO_2max, and BMI of Each Research Subject Group

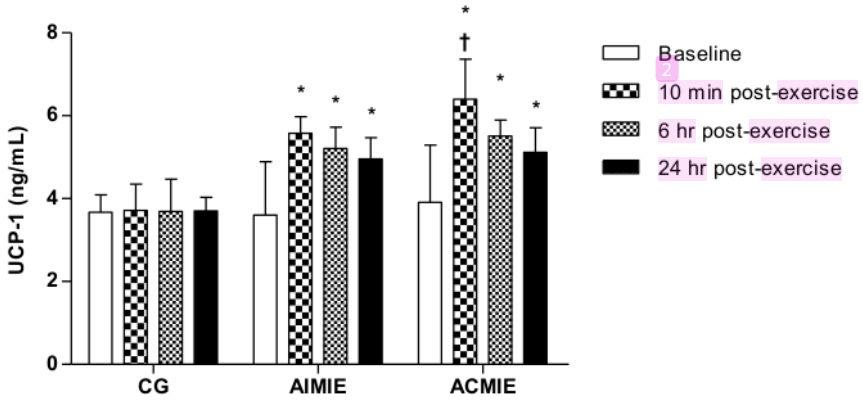


Figure 3. Pretest and Posttest UCP-1 Expression on Each Group
*Significant vs. baseline ($p \leq 0.05$). †Significant vs 24 hr post-exercise ($p \leq 0.05$).

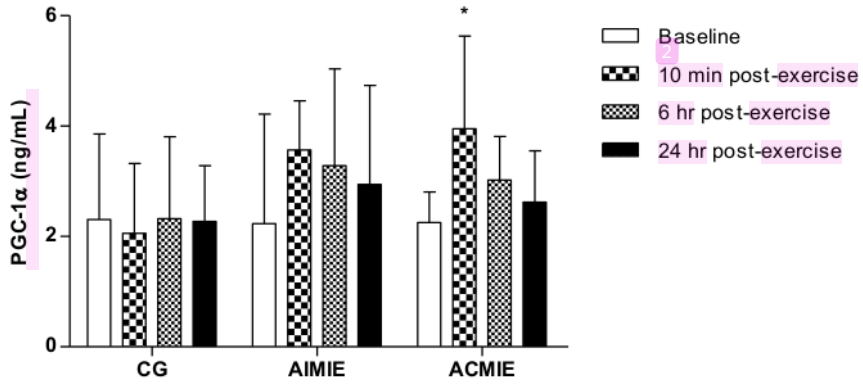


Figure 4. Pretest and Posttest PGC-1α Expression on Each Group
*Significant vs. baseline ($p \leq 0.05$).

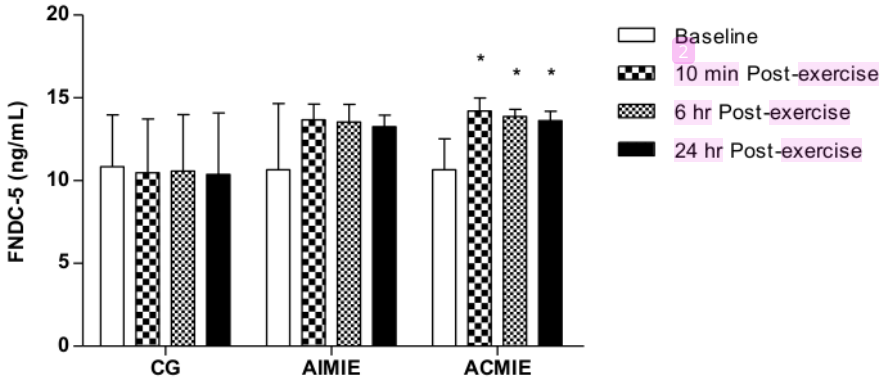
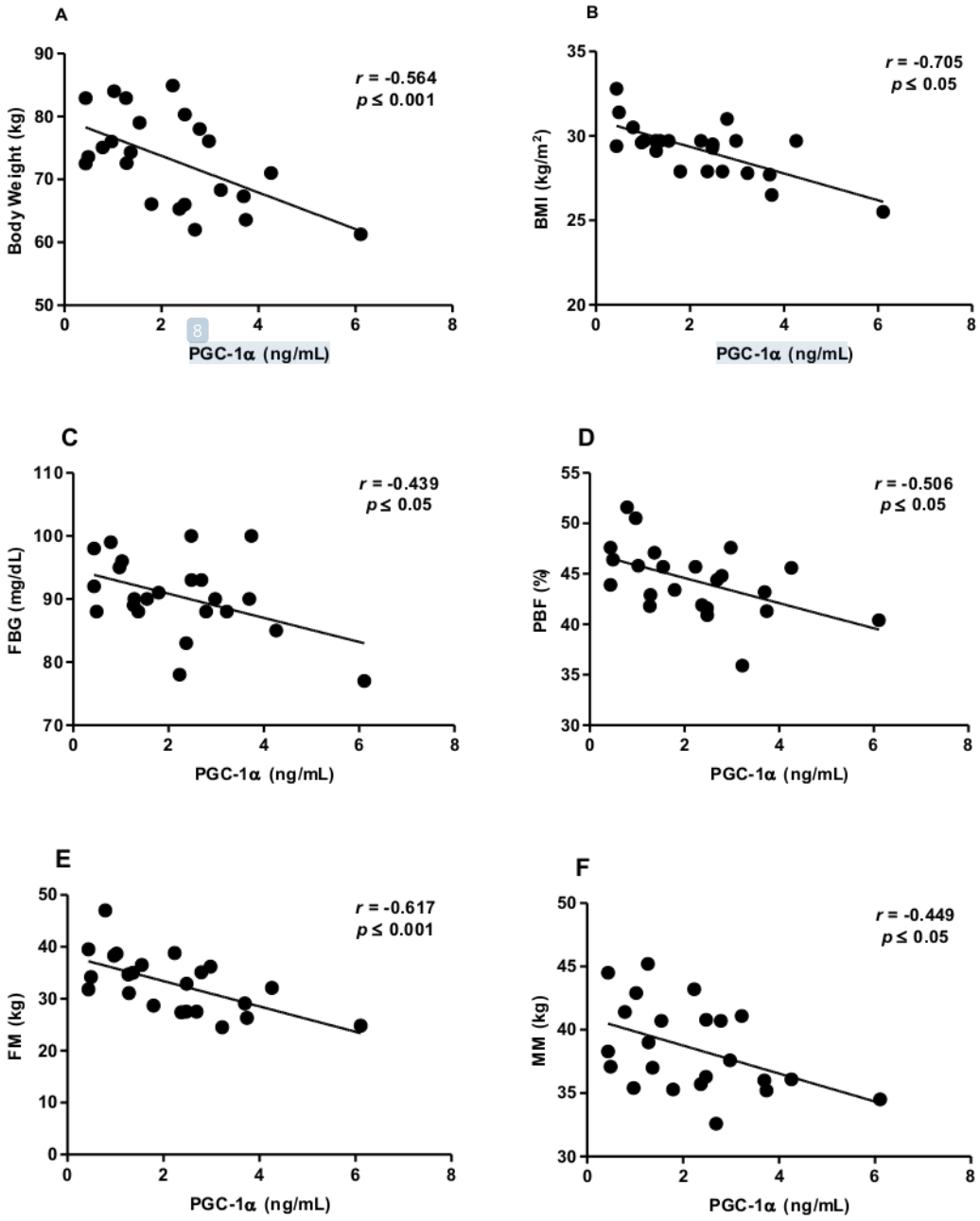


Figure 5. Pretest and Posttest FNDC5 Expression on Each Group
*Significant vs. baseline ($p \leq 0.05$).


A
Body Weight (kg)
r = -0.564
p ≤ 0.001
PGC-1α (ng/mL)
B
BMI (kg/m²)
r = -0.705
p ≤ 0.05
PGC-1α (ng/mL)
C
FBG (mg/dL)
r = -0.439
p ≤ 0.05
PGC-1α (ng/mL)
D
PBF (%)
r = -0.506
p ≤ 0.05
PGC-1α (ng/mL)
E
FM (kg)
r = -0.617
p ≤ 0.001
PGC-1α (ng/mL)
F
MM (kg)
r = -0.449
p ≤ 0.05
PGC-1α (ng/mL)

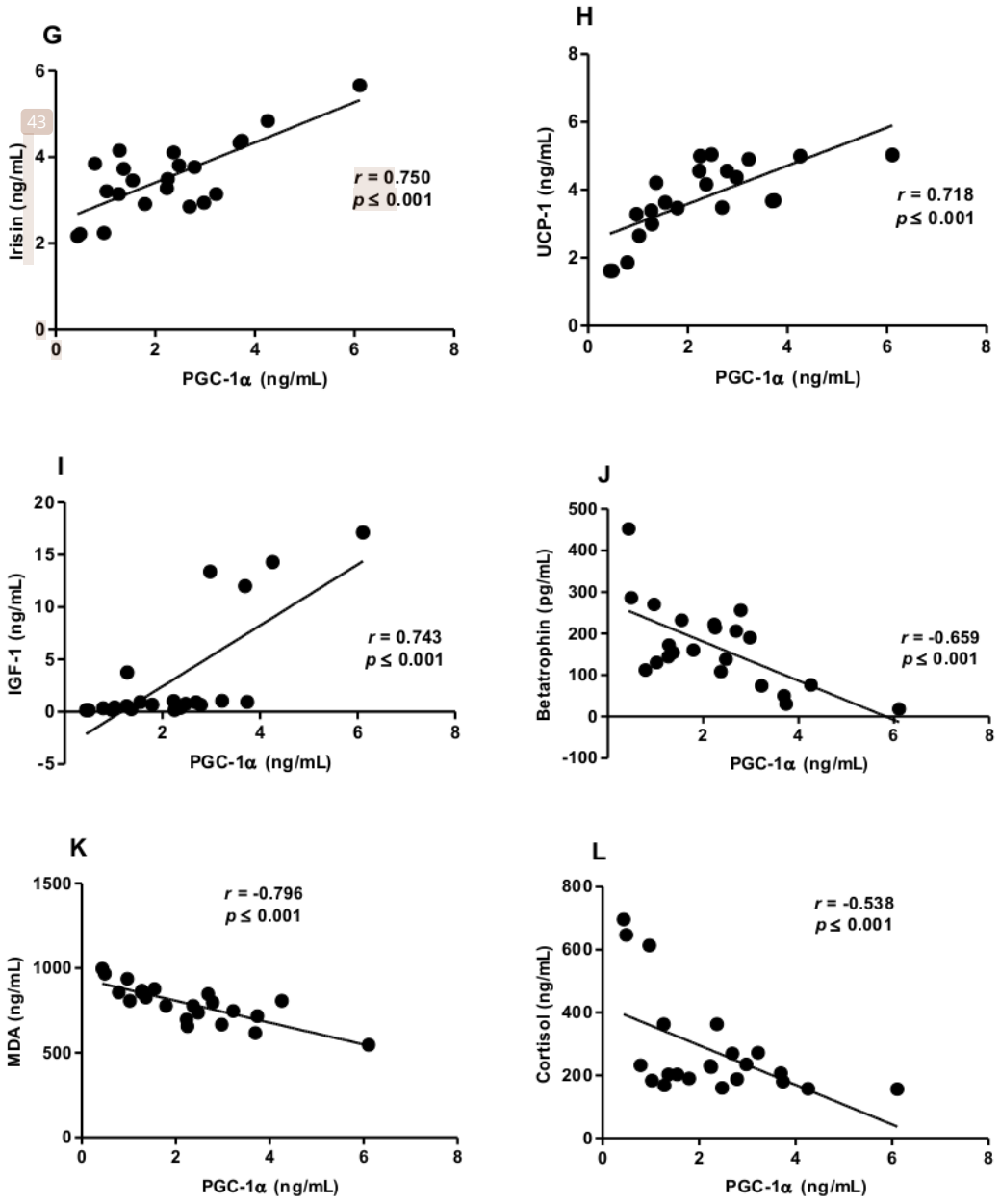


Figure 6. The relation between PGC-1α, anthropometric measurements, metabolism, and thermogenic genes, along with physiological and oxidative stress. The significant linear correlation between parameters was visualized in the plot model ($p \leq 0.05$). Picture **A.** Correlation between PGC-α and bodyweight; **B.** Correlation between PGC-1α and BMI; **C.** Correlation between PGC-1α with FBG; **D.** Correlation between PGC-1α and PBF; **E.** Correlation between PGC-1α and FM; **F.** Correlation between PGC-1α and MM; **G.** Correlation between PGC-1α and irisin; **H.** Correlation between PGC-1α and UCP-1; **I.** Correlation between PGC-1α and IGF-1; **J.** Correlation between PGC-1α and Betatrophin; **K.** Correlation between PGC-1α and MDA; and **L.** Correlation between PGC-1α and Cortisol.

Changes in the circadian cycle of thermogenic genes in this study present a decreasing trend at 6 hours to 24 hours after exercise compared to 10 minutes after exercise, but it remains higher than in the control group (Table 2 and Figure 3-5). Our results found coordinated circadian cycle changes in the thermogenic genes PGC-1α, FNDC-5, and UCP-1 at 10 minutes, 6 hours, and 24 hours after the interval and continuous exercise in obese female subjects. Previous studies also identify coordinated changes in expression of irisin, FNDC-5, and PGC-1α after 1 hour of exercise in mice in which the expression of these genes turns similar to the control group 24 hours after exercise [58]. However, in our study, 24 hours after exercise, the thermogenic gene expression of PGC-1α, FNDC-5, and UCP-1 remain higher than the control group. Previous studies have also reported changes in the circadian cycle of the thermogenic gene PGC-1α 6 hours after exercise [59]. Besides, the results of this study also find a positive correlation between PGC-1α and FDNC-5, irisin and UCP-1 (Table 3 and Figure 6). It signifies that thermogenic genes are interrelated and influence each other, with PGC-1α as the master regulator of biogenesis [62]. It is hypothesized that 24 hours after exercise, the thermogenic gene is expected to remain active. This condition is favorable and attractive for the browning process in maintaining homeostasis in response to decrease AMP/ATP ratio [63] and increase biogenesis in mitochondria [64]. A decrease in the AMP/ATP ratio leads to active AMPK, which is observed to occur 3 hours after exercise [59]. AMPK activation triggers activation of the PGC-1α gene receptor [61], stimulates an increase in FNDC-5, which then cleaves into circulating irisin to activate UCP-1 [65]. Consequently, PGC-1α-induced UCP-1 activation increases browning [46]. This process enhances energy generation through oxidative phosphorylation and energy expenditure [61]. It also improves the browning capacity, which can oxidize glucose and lipids as an energy source [4]. Thus, it becomes an attractive target for controlling obesity [66].

Furthermore, our results indicated that circadian cycle changes in thermogenic gene expression are detected 6 hours and 24 hours after exercise. It is intriguing to see that the thermogenic gene cycle is non-permanent and transient (Figure 3-5). Previous studies have also reported changes in the thermogenic gene cycle PGC-1α, FNDC-5, and UCP-1 decreased after acute exercise [53] and chronicles [49]. The activity of thermogenic genes is essential as a regulator of energy metabolism [67] to enhance mitochondrial biogenesis [61] and increase oxidative phosphorylation [33]. This is presumed to be able to prevent the development of obesity [11]. Therefore, previous studies recommend that exercise should be done repeatedly and continuously [68], with the right intensity [32]. This will improve the PGC-1α, FNDC-5, and UCP-1 thermogenic genes [22]. The increasing thermogenic gene on exercise balances glucose through affected gene expressions, such as glucose transporter type 4 (GLUT4) and peroxisome proliferator-activated receptor-alpha, which play a role in regulating glycogenase (PCK1) and gluconeogenesis (PYG) [23]. The results of this study also identify a negative correlation of the PGC-1α thermogenic gene with betatrophin (Table 3 and Figure 6). Similarly, previous studies have also reported an increase in PGC-1α expression followed by a decrease in betatrophin [69]. Decreased expression of betatrophin affects the active lipoprotein lipase (LPL) enzyme [25] and increases the use of triglycerides as an energy source [23]. Consequently, it increases oxidative phosphorylation in the mitochondria [70]. Therefore, the PGC-1α, FNDC5, and UCP-1 thermogenic genes activities must be maintained to increase browning activity with increased thermogenesis [1]. The increase in thermogenesis affects the increasing energy expenditure through oxidation so that it decreases the fat deposits [22]. However, exercise must be done with the right intensity and according to ability [11] considering that it also carries the potential to increase the physiological stress hormone cortisol [71].

Importantly, the correlation analysis results in this study indicate a negative relationship between thermogenic gene expression and physiological and oxidative stress (Table 3 and Figure 6). Physiological stress reduces ATP, increases the ATP/AMP ratio, and activates AMPK, thereby inhibiting PGC-1α expression [72]. It also causes metabolic disorders and lowers immunity [73], and is a risk factor for increased disease and a cause for exercise maladaptations [74]. On the other hand, oxidation stress is a cause of tissue damage, especially in the mitochondrial membrane [75]. This signifies that thermogenic genes also regulate antioxidant gene expression in the mitochondria to prevent oxidative injury and mitochondrial dysfunction [33]. However, in obese subjects, thermogenic genes such as the PGC-1α gene and UCP-1 are lower than in normal-weight subjects [76]. This low thermogenic gene may also be related to the low IGF-1 as a regulator of muscle mass and muscle hypertrophy [77]. The greater the muscle mass increases the PGC-1α expression and the biogenesis ability [78]. Obese subjects also had low UCP-1 thermogenic gene activity [79], along with minimum influenced mitochondrial function and browning [34]. Obese subjects are observed to have lower antioxidant activity compared to normal-weight subjects, so that they have higher chance to get oxidative stress [33]. Obese subjects also have a relatively high level of physiological stress [80], while exercise is classified as a potential stressor for the body [30]. Therefore, exercise for these people must be properly regulated, with an appropriate and measured intensity [81]. In addition to improving physical fitness [32], immunity health [30], and increase endorphins [82], exercise also plays a role in improving the performance of thermogenic genes, which

prevents the increase in malondialdehyde (MDA) [83]. Thus, the exercise is essential as a non-pharmacological strategy and method [84]. However, the exercise intensity must be measured and following the body's ability, so that exercise can be enjoyable and cause no stress [72]. A measurable exercise is predicted to have an optimal effect on skeletal muscle performance and energy metabolism [28]. Exercise has an appeal for society for lifestyle modifications that contribute to preventing obesity, metabolic syndrome and metabolic disorders, and increasing the physiological capacity of the body [11]. Acute moderate-intensity interval and continuous exercise in this study contribute to new theoretical development as a non-pharmacological and physiological approach in preventing obesity and reducing its risk factors. Exercise with moderate-intensity intervals continuously changes the circadian cycle of thermogenesis genes, positively impacting the improvement of metabolic health in obese subjects. Therefore, moderate-intensity exercise is the proper workout that follows the subject's ability, so it will be a strategic and attractive approach for vulnerable or untrained groups in preventing obesity and reducing its risk factors. The use of interval and continuous exercise with moderate-intensity in obese female subjects is a new approach expected to become a model for active lifestyle modification in preventing obesity in the future.

Even though our results demonstrate a significant effect on thermogenic genes' activity in the circadian cycle of obese individuals, this research still has some limitations. First, the research did not measure the circadian cycle of thermogenic genes that changes every hour, so the thermogenic gene's circadian peak was not investigated. Second, this research only employed obese subjects. It did not compare the changes in the circadian cycle of thermogenic genes with healthy subjects or normal-weight subjects after acute exercise. However, the circadian cycle pattern of thermogenic genes changes in obese individuals and its relationship with stress parameters can provide primary data. Besides, it also gives an initial picture that changes in the circadian cycle of thermogenic genes have an extensive effect on metabolism and can be used as a strategy for non-pharmacological therapy in preventing and treating, obesity, metabolic syndrome, and other metabolic disorders.

Conclusions

Acute and continuous exercise with moderate intensity can increase the expression of thermogenic genes in the circadian cycle of obese subjects. Hence, acute exercise with moderate-intensity may be a model for developing potential non-pharmacological therapies to prevent, treat and control the increase in obesity and other metabolic disorders.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of interest

The authors declare that they have no competing interests.

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