

Secretion Of PGC-1 α By Modulating Physical Exercise To Protect Improving Obesity Prevalence

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ABSTRACT

Physical exercise can modulate the secretion of peroxisome proliferation activated receptor γ coactivator-1 α (PGC-1 α) as a prevention strategy to increase the prevalence of obesity. This study aims to analyze the response of physical exercise as a modulation of PGC-1 α to protect against the increasing prevalence of obesity. This research is a true experimental design with the randomized pretest-posttest control group design using 15 obese women aged 18-22 years, Body Mass Index (BMI) 25-35 kg/m², normal blood pressure, Resting Heart Rate (RHR) normal, VO_{2max} 25-35 ml/kg/min and randomly divided into three groups, namely CONT (n=5, Control Without Intervention), MIIE (n=5, Moderate Intensity Interval Exercise) and MICE (n=5, Moderate Intensity Continuous Exercise). The intervention was carried out at 07.00-09.00 a.m. MIIE and MICE interventions carried out for 40-45 minutes using a treadmill. Pre-exercise blood sampling and 10 minutes post-exercise. Measurement of PGC-1 α levels used the Enzyme-Linked Immunosorbent Assay (ELISA) method. Data analysis techniques used ANOVA test and LSD post hoc test with the Statistical Package for Social Science (SPSS). The results obtained mean PGC-1 α pre-exercise levels at CONT (1.733 \pm 1.651) ng/mL, MIIE (2.465 \pm 1.334) ng/mL and MICE (2.198 \pm 0.853) ng/mL (p=0.706). The mean PGC-1 α post-exercise levels in CONT (2.107 \pm 1.603) ng/mL, MIIE (2.753 \pm 1.093) ng/mL and MICE (2.566 \pm 0.843) ng/mL (p=0.717). Based on the results of the study it is concluded that there are no significant differences in the mean levels of PGC-1 α pre-exercise and post-exercise in all groups (P>0.05). It is recommended to do further research by providing moderate intensity treadmill exercise intervention which is carried out chronically to increase PGC-1 α levels.

Keywords: PGC-1 α levels, moderate intensity interval exercise, moderate intensity continuous exercise, obese women

Received May, 23, 2020; Revised June 16, 2020; Accepted June 28, 2020



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BACKGROUND

Obesity is still a global concern, because the prevalence of obesity continues to increase significantly (Rachmi *et al.*, 2017). In 2015, the prevalence rate of obesity in the world reached 39% of the total population of all countries. Increased obesity prevalence in detail is divided into developed and developing countries. Increased prevalence in developed countries experienced a significant increase from 1980 amounting to 45.3% to 64.2% in 2015. Increased prevalence of obesity in developing countries experienced a significant increase from 1980 amounting to 10.9% to 24.3% in 2015 (Chooi *et al.*, 2019), if the trend of bad lifestyle continues, then it is estimated that in 2030 will increase to 38% overweight and 20% obese (Kelly *et al.*, 2008). In Indonesia, based on the results of the Basic Health Research (Riskesdas) in 2018, the prevalence of obesity at the age of 18 years old experienced a significant increase from 2007 reaching 10.5% to 14.8% in 2013 and in 2018 increasing to 21.8% (Riskesdas, 2018). The increasing prevalence of obesity in women tends to be higher than in men (Garawi *et al.*, 2014). The increasing prevalence of obesity has been very worrying and poses a very serious threat to public health, especially women (Lobstein and Jackson, 2006).

Obesity is caused by an energy imbalance that results in one of them metabolic syndrome (Collision *et al.*, 2010). Several factors as a cause of obesity include genes (Bell *et al.*, 2005), inactive lifestyle, stress, eating habits and fast food (junk food) (Collision *et al.*, 2010). This situation can unconsciously reduce the functional ability of the body as a public health threat (Dinas *et al.*, 2017). Decreased functional ability of the body can change the body's homeostasis with the onset of metabolic syndrome diseases, such as type 2 diabetes mellitus, cardiovascular disease and hypertension (Lobstein and Jackson., 2006) which are worse than these conditions can cause premature death (Collision *et al.*, 2010). Therefore, a non-pharmacological approach is needed to gradually reduce the prevalence of obesity. Exercise-based weight loss method by modulating browning white fat to brown fat mediated by peroxisome proliferation activated receptor γ coactivator-1 α (PGC-1 α) (Dinas *et al.*, 2017) is the right method to be used in preventing the increase in obesity prevalence.

PGC-1 α plays an important role as co-transcription which facilitates various transcription factors to regulate complex tissues, such as being involved in regulating carbohydrate and lipid metabolism in energy formation (Jung and Kim., 2014). Muscle contractions are mediated with Ca^{2+} to attach actin and myosin which are conditions for contractions (Sugiharto, 2012). Ca^{2+} builds up in the muscles to stimulate adenosine monophosphate protein kinase (AMPK) which plays a role in stimulating the enzyme mitogenactivated protein kinase (MAPK) or under another name P38 for energy formation by stimulating PGC-1 α containing disitosisol which plays a role in secreting Protein Fibronectin-Type III Domain Containing 5 enzymes (FNDC5), then FNDC5 undergoes the process of breaking down proteins that will be released into the bloodstream called Irisin (Rowe *et al.*, 2010). PGC-1 α has an important role in converting white fat to brown fat through modulating irisin (Dinas *et al.*, 2017).

Increased levels of PGC-1 α can be stimulated through exercise (Jung and Kim, 2014). Exercise with moderate and high intensity has been shown to increase PGC-1 α levels (Dinas *et al.*, 2017), both acute and chronic. Likewise, endurance training with moderate intensity performed acutely increases PGC-1 α levels (Little *et al.*, 2010). Previous studies also showed the same results that endurance training and strength with moderate intensity increased PGC-1 α levels (Norheim *et al.*, 2014). For this reason, the

purpose of this study is to analyze the acute response of moderate interval training and continuous intensity to increasing levels of PGC-1 α in obese women.

METHODS

This research is a true experimental design with the randomized pretest-posttest control group design using 15 obese women aged 18-22 years old, Body Mass Index (BMI) 25-35 kg/m², normal blood pressure, Resting Heart Rate (RHR) normal, VO_{2max} 25-35 ml/kg/min and randomly divided into three groups, namely CONT (n=5, Control Without Intervention), MIIE (n=5, Moderate Intensity Interval Exercise) and MICE (n=5, Moderate Intensity Continuous Exercise). All of the research procedures were approved by the Medical Research Ethics Commission of the Faculty of Medicine, University of Brawijaya Malang number 26/EC/KEPK-S1/02/2020.

Measurement of height and weight used GEA ZT-120. VO_{2max} measurements used Astrand 6-minute cycle test method using an ergo-cycle (Monark 828 E, Version 1010 Art. No: 7950-296, Vansbro, Sweden). Heart rate monitoring used Polar (Polar H10 Heart Rate Sensor, USA, Inc.). Blood pressure was measured using an OMRON digital blood pressure monitor (OMRON Model HEM-7130 L, Omron Co.).

Blood sampling was done in 4 ml cubital veins (Daskalopoulou *et al.*, 2014). When taking blood, the subject is in a sleep position. Blood sampling was done 2 times pre-exercise and 10 minutes post-exercise. The blood was centrifuged for 15 minutes at 3000 rpm (Tsuchiya *et al.*, 2014; Daskalopoulou *et al.*, 2014). Measurement of PGC-1 α levels used the Enzyme-Linked Immunosorbent Assay (ELISA) kit (Catalog No. E-EL-H1359; Elabscience, Inc., China, 2019) with a standard curve range of 0.16-10 ng/mL and the level of sensitivity of the PGC-1 α in the kit 0.10 ng/mL.

MIIE intervention was carried out by running on a treadmill with moderate intensity 60-70% HR_{max} for 45 minutes with details of 5 minutes warming (50-60% HR_{max}), 35 minutes core (5 minutes work (60-70% HR_{max}) interspersed with recovery active on the treadmill for 2.5 minutes (50-60% HR_{max}) performed 5 repetitions) and 5 minutes of cooling (50-60% HR_{max}). MICE intervention is carried out by running on a treadmill with an intensity of 60-70% HR_{max} for 40 minutes with details of 5 minutes warming (50-60% HR_{max}), 30 minutes of core carried out continuously (60-70% HR_{max}) and 5 minutes cooling (50-60% HR_{max}). The intervention was carried out at 07.00-09.00 a.m using a treadmill (Richter Treadmill Semi-Commercial Evolution (4.0 hp dc)).

Data analysis techniques used Statistical Package For Social Science (SPSS) software version 21 (Chicago, IL, USA). The normality test uses the Shapiro-Wilk test, while the homogeneity test uses the Levene test. Data that were normally distributed and had a homogeneous variant were tested using the ANOVA test and continued with a post hoc LSD test with a significant level ($P < 0.05$). All data are displayed with mean \pm SD.

RESULT

The results of descriptive analysis of the research subjects' characteristics can be seen in table 1 below.

Table. 1 Research Subjects' Characteristics.

Table 1 Research Subjects Characteristics							
Variable	Group						<i>p-value</i>
	CONT		MIIE		MICE		
	Mean	SD	Mean	SD	Mean	SD	
Physiological							
SBP (mmHg)	113.333	5.164	113.333	5.164	111.667	4.083	0.444

DBP (mmHg)	76.667	5.164	76.667	5.164	73.333	5.164	0.668
RHR (bpm)	78.14	11.35	81.37	14.68	78.38	8.45	0.835
MHR(bpm)	199.43	0.98	199.50	1.41421	199.38	0.74	0.974
Anthropometry							
BMI (kg/m ²)	29.850	1.601	28.850	1.992	29.017	1.583	0.346
Age (years)	20.667	1.033	21.000	1.414	20.667	0.817	0.776
Physical							
VO _{2max} (ml/kg/min)	27.407	2.374	26.270	1.104	27.383	1.348	0.146

Note: SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, HR: Resting Heart Rate, MHR: Maximum Heart Rate, BMI: Body Mass Index, VO_{2max}: Volume Oxygen Maximum.

Based on Table 1, ANOVA test showed that there are no significant differences in the mean data characteristics of research subjects in all groups. The results of the analysis of PGC-1 α levels in each group can be seen in Table 2.

Table. 2 Results of Analysis of PGC-1 α Levels in Each Group

PGC-1 α Level	Group			ANOVA P-value
	CON (n=5)	MIIE (n=5)	MICE (n=5)	
Pre-exercise	1.733 \pm 1.651	2.465 \pm 1.334	2.198 \pm 0.853	0.706
Post-exercise	2.107 \pm 1.603	2.753 \pm 1.093	2.566 \pm 0.843	0.717

Note: All data is displayed with Mean \pm SD.

Based on Table 2, it is showed that there is no significant difference in the mean PGC-1 α levels between pre-exercise and post-exercise in all groups ($P>0.05$).

DISCUSSION

Based on Anova test on the characteristics of the research subjects, it is showed that there is no significant difference in the average characteristics of the research subjects in all groups with a value of ($P>0.05$). The study is in line with the results of research conducted by Frank *et al.* (2003) concluded that there were no significant differences in the characteristics of research subjects which included BMI, Body Fat (BF) and VO_{2max}. This indicates that the researcher controls the data characteristics of the research subjects, so that in all groups there is no difference. PGC-1 α increases with several models, one of which is exercise (Dinas *et al.*, 2017). Training has an important role in increasing the level of PGC-1 α . Increased levels of PGC-1 α are in citosol and increased levels of PGC-1 α are in the nucleus (Wright *et al.*, 2007) higher increases in the nucleus (Little *et al.*, 2010).

Anova test showed that there is no significant difference in the mean pre-exercise PGC-1 α levels in all groups ($P>0.05$). This shows that in this study using the same subject that is obese women in all groups (CON, MIIE and MICE), so the levels of PGC-1 α pre-exercise did not show a significant difference. Therefore, if there is a change in PGC-1 α levels purely due to the influence of the given exercise. Based on Table 2, ANOVA test results showed that there are no significant differences in PGC-1 α post-exercise levels in all groups ($P>0.05$). However, when it is viewed from the average value of MIIE, it tends to have a higher PGC-1 α level compared to MICE and CON. These results are in line with the results of research conducted by Norheim *et al.* (2014) concluded that there was no significant increase in mean PGC-1 α levels after moderate intensity interval training in obese subjects. Likewise research conducted by Leick *et al.* (2008) using a sample of

wistar rats that were given moderate continuous intensity exercise interventions that were carried out acutely using a treadmill also did not show a significant increase in mean PGC-1 α levels. However, other studies have found different results that the administration of moderate continuous intensity exercise significantly increases PGC-1 α levels 3 hours and 24 hours after exercise intervention (Shirvani and Arabzades, 2018). But these results contradict the results of research conducted by Taylor *et al.* (2016) using subjects aged 25-35 years old who were given anaerobic training with interval and continuous methods for 3 weeks did not show a significant increase in the mean PGC-1 α levels. Based on previous research, it is showed that the increase in PGC-1 α occurs after exercise 1, 2 and 3 hours (Akimoto *et al.*, 2004) 5 hours (Gibala *et al.*, 2009).

Exercise is a stimulant that is very physiological and involves all body systems, whether muscular, nervous, metabolic systems or the hormonal system (Sugiharto, 2012). The stimulation will be responded by the body in creating homeostasis by secreting myokines. Myokin has an important role as endocrine, paracrine and autocrine (Shirvani and Arabzadeh, 2018). Exercise has been shown to activate the phenotype of brown adipose tissue by increasing PGC-1 α secretion (Popov *et al.*, 2014). PGC-1 α is a transcript regulator that facilitates various transcription factors to regulate the network of highly complex genes involved in mitochondrion changes and the formation of brown adipose tissue (Dinas *et al.*, 2017).

Long duration exercises are indicated by contraction of skeletal muscle. Muscle contraction is related to the type of muscle fiber types that are heterogeneous and the recruitment of fiber types depends on the intensity during exercise (Altenburg *et al.*, 2007). Type of muscle fibers I and II with exercise has an important role and both are related to the exercise. Wang and Sahlin (2012) study of muscle fiber types I and II with moderate intensity had a significant difference between the use of muscle fiber types and had no difference in the role of secreting PGC-1 α . Muscle fiber type I as the dominant type of muscle fiber is used for long duration sports (Stockdale, 1997) with relatively high mitochondrial and oxidizing properties which is estimated to 20% and 10% (Jung and Kim, 2014).

Skeletal muscle plays an important role in exercises stimulated by the brain. The limbic system under the hypothalamus has an important role in digging up memories to make movements that have been performed. Limbic will stimulate the HPA axis (Thomas and Lena., 2010) to regulate the endocrine system and deliver impulses to the cortical premotor as a skeletal muscle drive (Shirvani and Arabzadeh, 2018). In order to contract skeletal muscle, the cortex premotor will stimulate Ca²⁺ in the muscle as an actin and myosin attachment that will stimulate CaMK to transfer phosphate ATP to serine or serotonin residues (Swulius and Waxham., 2008) with the passage of time the ATP level will be low, which will phosphorylate the ATP phosphate to serine or serotonin residues (Swulius and Waxham., 2008). AMPK (Taylor *et al.*, 2016) to supply energy by stimulating PGC-1 α which plays a role in glucose and fatty acid metabolism (Ljubicic *et al.*, 2010) plays an important role in mitochondrial biogenesis (Pilegaard *et al.*, 2003).

MIIE training in terms of energy system expenditure has greater expenditure than MICE training (Taylor *et al.*, 2016). This situation is a proof that MIIE training in Ca²⁺ expenditure is greater which can affect energy metabolism in increasing CaMK levels will increase ATP levels as energy in the body (Jung and Kim, 2014). Deposits of ATP will decrease and phosphorylate MAPK, stimulate PGC-1 α as the formation of ATP for the next energy (Karatzeferi *et al.*, 2001). Increased MAPK levels will also increase PGC-1 α levels (Taylor *et al.*, 2016) the increase is 53% in MIIE (Greenhanff *et al.*, 1994).

CONCLUSION

Based on the results of the study, it is concluded that there are no significant differences in the mean levels of PGC-1 α pre-exercise and post-exercise in all groups ($P>0.05$). It is recommended to conduct further research by providing moderate intensity treadmill exercise intervention which is carried out chronically to increase PGC-1 α levels.

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