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The Expression of Visceral Fat Uncoupling Protein-1 is Higher in Moderate-Intensity Swimming than in Low or High-Intensity Swimming in Mice

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Abstract

To prove the effect of exercise intensity on fat browning process through increased level of muscle peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α) and visceral fat's uncoupling protein 1 (UCP1) expression in male mice.

The research used a posttest only control group design. Mice were divided into 4 groups: K1 (control), K2 (mild-intensity swimming with 3% body weight loaded), K3 (moderate-intensity swimming with 6% body weight loaded) and K4 (high-intensity swimming with 9% body weight loaded). The intervention was carried out for four weeks, three times a week. Level of PGC-1α was measured by ELISA of gastrocnemius muscle, and visceral fats UCP1 expression measured by immunohistochemistry. There were differences level of muscle PGC-1α in K1 (1.58±0.29) pg/mL, K2 (4.71±0.31) pg/mL, K3 (5.42±0.34) pg/mL, and K4 (3.34±0.35) pg/mL with p=0.00 (p<0.05). The highest PGC-1α level was found in the group given moderate-intensity swimming (K3). Morever, there were differences of the visceral fats UCP1 expression in K1 (5.47±0.83) IRS/LP, K2 (7.23±1.57) IRS/LP, K3 (9.17±1.65) IRS/LP, and K4 (6.93±1.42) IRS/LP with p=0.00 (p<0.05). Variation of exercise intensity affects level of muscle PGC-1α and the expression of visceral fat's UCP1 in male mice. Moderate-intensity exercise has the highest level of muscle and visceral fat UCP1 expression.

Experimental article (J Int Dent Med Res 2021; 14(2): 00-00)

Keywords: Exercise intensity, swimming, PGC-1α, visceral fat UCP1, mice

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Introduction

Obesity is a metabolic disease reaching epidemic proportions.[1] Obesity is a disease with a high risk of the emergence of severe health problems that will improve public health in the world.[2] The cause of obesity is due to multifactorial, but common factors contribute to weight gain, an imbalance between energy consumption and energy utilization.[3,4] Lifestyle modification approved is one of the cornerstones in the management of obesity.[2] Lifestyle modification with non-pharmacological goals based on exercise is an appropriate strategy.[5] Fat browning is one way to increase energy expenditure.[6]

Changes in white fat cells white adipose tissue (WAT) that resemble brown fat cells brown adipose tissue/beige adipose tissue (BAT) occur in the process of fat browning.[7] During the fat browning process, fat accumulation in the body can be prevented by increasing the energy output regulated by BAT. The series of fat browning processes also triggers increased expression of uncoupling protein 1 (UCP1) adipose cells to increase calories lost through regulation of thermogenesis and heat release processes.[8] The storage of surplus calories in the body is regulated by WAT, while BAT regulates the energy expenditure function via the thermogenesis mechanism. Changes in WAT cells resembling BAT cells can occur with an

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increase in UCP1 expression and mitochondrial biogenesis.[8] This process will later produce beige adipose tissue which has a role to prevent fat accumulation by increasing energy output.

Exercise is one of the many efforts to overcome overweight. During exercise, the secretion of peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α) muscle will increase through AMPK activation in the process of fat browning.[9,10] Transformation of white or brown fat cells is regulated by PGC-1α, which has a major role in this process. PGC-1α can activate UCP1 strongly in non-BAT cells. In addition, PGC-1α also induces UCP1 gene expression and mitochondrial biogenesis when exposed to white fat cells.[11] Biogenesis process occurring during exercise is expected to increase the number of mitochondria that are in fat cells.[12]

There are not yet findings showing the role of exercise intensity in fat cells in increasing energy expenditure. For this reason, research was conducted on male mice (*Mus musculus*) who were given mild, moderate and high-intensity exercise interventions to identify the effect of exercise intensity on fat browning events. This is useful to explain the effect of exercise intensity on changes in beige adipose tissue along with its mechanism which has an important role in energy homeostasis and fat metabolism.

Materials and methods

This study was conducted by posttest only control group design under the approval of Medical Research Ethics Committee Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia (188/EC/EPK/FKUA/2016). Thirty-two mice (BALB/c) aged 3–4 months, 20–30 grams, acclimatized for a week and maintained in some cages in the room temperature of 25–30°C, with adequate food and drinking water. The study had been held on January to December 2018 in Laboratory of the Department of Biochemistry, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.

The 32 mice were divided into 4 groups, they were K1 as control, K2 with mild-intensity swimming with 3% body weight loaded, K3 with moderate-intensity swimming with 6% body weight loaded and K4 with high-intensity swimming with 9% body weight loaded. Swimming was performed three times a week for four weeks, every at 3 pm, with each load and done by calculating the maximum duration of swimming ability each mice. Duration of exercise was taken from 80% of the maximum time achieved by each mouse.

Animal weights were measured in all groups, before and after experiment using a torbal (torsion balance) scales Camry EK3250 in gram using with precision one digit behind the comma. In the end of the experiment, mice were eventually terminated and gastrocnemius musculus was taken in the right leg and visceral fat from the abdominal cavity. Gastrocnemius muscle was synchronized to take tissue fluid to measure PGC-1α levels by ELISA. UCP1 expression of visceral fat was examined using immunohistochemistry by counting the number of cells expressing it per field of view with 400x magnification using the Nikon H600L microscope; DS Fi2 camera is 300 megapixels. Data were analyzed for distribution normality with Saphiro-Wilk test, variance homogeneity with Lavene test, different tests using one way Anova and LSD. Data analysis used SPSS version 17.

Results

Pretreatment, post-treatment body weight and changes in body weight can be seen in Table 1. In the initial conditions, body weight in all groups was homogeneous, and there were differences at the end of treatment. Most weight loss in K3 was at moderate-intensity swimming.

Groups	n	Body weight (g)			One-Way ANOVA
		Pretest	Posttest	Δ	
K1	8	32.80 ± 2.04[a]	35.00 ± 2.21[a]	2.20 ± 1.03[a]	p=0.00
K2	8	31.67 ± 2.58[a]	27.50 ± 3.27[b]	-4.17 ± 2.14[b]	
K3	8	33.17 ± 1.94[a]	26.67 ± 2.94[b]	-4.83 ± 2.64[b]	
K4	8	33.00 ± 3.85[a]	30.33 ± 3.93[b]	-2.67 ± 2,25[b]	

Table 1: Body weight at the beginning and end of the treatment and change in body weight.
Different superscripts show significant differences in LSD with p<0.05

Table 2 shows the differences in PGC-1α levels in the gastrocnemius muscle after treatment. After swimming for four weeks with a frequency of 3 times/week, PGC-1α levels were higher in all treatment groups when compared to control. The highest PGC-1α level was found in the group given moderate-intensity swimming (K3), although there was no significant difference between K3 and K4.

Groups	n	Levels of PGCα (pg/mL)	One-Way ANOVA
K1	8	1.58 ± 0.29[a]	p=0.00
K2	8	4.71 ± 0.31[b]	
K3	8	5.42 ± 0.34[c]	
K4	8	3.34 ± 0.35[d]	

Table 2: PGCα levels post-treatment.
Different superscripts show significant differences in LSD with p<0.05.

The expression of UCP1 visceral fat after treatment can be seen in Table 3 and Fig. 1. In all treatment groups, UCP1 expression was higher when compared to the control group. The expression of UCP1 in mice given a moderate intensity swimming was significantly higher in all treatment groups.

Groups	n	UCP1 expression of visceral fat	One-Way ANOVA
K1	8	5.47 ± 0.83[a]	p=0.00
K2	8	7.23 ± 1.57[b]	
K3	8	9.17 ± 1.65[c]	
K4	8	6.93 ± 1.42[b]	

Table 3. Expressions of UCP1 in visceral fat after treatment. Different superscripts show significant differences in LSD with p<0.05

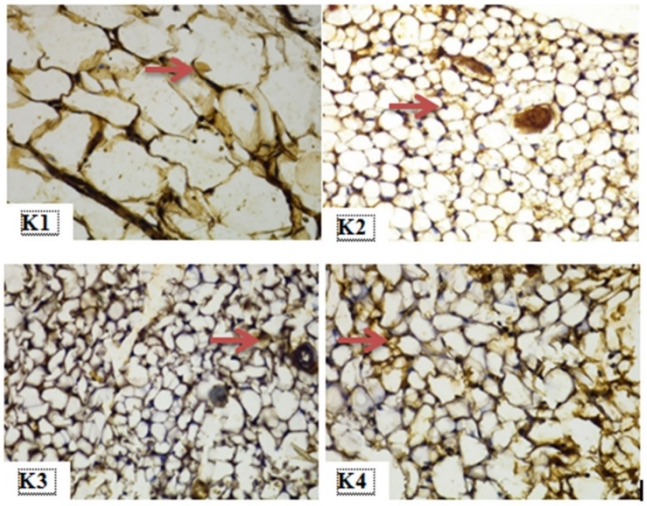

Figure 1. The expression of UCP1 visceral fat cells in mice (arrows); K1 = control group, K2 = mild-intensity swimming treatment group, K3: moderate-intensity swimming treatment group, K4 = high-intensity swimming treatment group (histochemical immuno staining, 400x magnification; Nikon H600L microscope; DS Fi2 camera 300 megapixels).

Discussion

Body weight of mice in all swimming groups with different intensities decreased, while in the control group increased body weight.

The most significant weight loss occurred in the moderate-intensity swimming group, followed by the mild-intensity swimming group, and the last was the high-intensity swimming group. Weight loss is related to energy output. The higher the energy expended, the greater the weight loss. The energy expended must be higher than the intake for weight loss.[3] The energy expended by prolonged exercise shows a more significant contribution to weight loss.[13] Efforts for each treatment group were given based on the percentage of body weight of mice (3% for the mild-intensity swimming group; 6% for the moderate-intensity swimming group; 9% for the high-intensity swimming group). This is based on research methods that have been done before.[14] Meanwhile, swimming duration is determined 80% of the maximum time the ability to swim mice.[15,16] During the study, the most extended swimming duration was the mild-intensity swimming group with an average of 16.30 seconds, followed by a moderate intensity of 14.03 seconds, only the last was a high intensity of 6.77 seconds. Thus, even though the effort is charged a large amount, but the duration to make an effort is the shortest. Because of this, when high-intensity swimming was given, the energy output was smaller than the other groups.

The results of the analysis prove that swimming exercises with various intensities increase PGC-1α levels more than the control group. That is because exercise can increase the secretion of muscle PGC-1α through AMPK activation, which plays a role in the process of fat browning. The PGC-1α substance is the primary regulator of a cell transforming into white or brown fat cells. Some data indicate that PGC-1α is likely to play a role in this process [17]. First, PGC-1α is the only protein that can activate UCP1 strongly in non-BAT cells. Second, when exposed to white fat cells, PGC-1α induces the expression of the UCP1 gene and mitochondrial biogenesis, two essential aspects in brown fat cells.[18]

Skeletal muscles are endocrine organs that can communicate with other tissues via myokines, which are released into the circulation during physical exercise.[19] PGC-1α, a molecule involved in the regulation of gene expression, plays an essential role in the maintenance of glucose, lipids, and energy homeostasis.[9] PGC-1α integrates the activity of the main signaling pathway that is important in muscle contraction. Thus, the levels of PGC-1α and protein transcription increase after physical exercise.

PGC-1α is induced in skeletal muscles by physical exercise and stimulates many positive effects during physical exercise.[20]

UCP1 expression in visceral fat in all swimming groups was higher than in the control group. Moreover, linearly with PGC-1α levels, the highest UCP1 expression was found in the moderate-intensity group. The results of this study are in line with previous studies in which visceral fat browning occurs in physical exercise for one week,[21] and physical exercise for 60 minutes/day for more than seven days can improve UCP1 regulation in BAT.[22] Bostrom et al. showed that skeletal muscle, at elevated levels of PGC-1α, induced the expression of fibronectin type III domain containing 5 (FNDC5) protein, which after cleavage was secreted into blood vessels as irisin. Irisin binds to the surface of white adipocytes, induces UCP1 expression, and stimulates changes in white fat cells into BRITE cells.[23] An increase follows this change in total energy expenditure, weight loss, and increased glucose intolerance.

Apart from being influenced by PGC-1α, increased expression of UCP1 may also be caused by increased stimulation of sympathetic nerves during exercise that stimulates the release of norepinephrine or epinephrine.[24] Norepinephrine binds to beta-adrenergic receptors combined with protein G for activation of adenylate cyclase; this contributes to the activation of cAMP, protein kinase A, and p38MAPK, then activates the enzyme stimulation of lipolysis, adipose triacylglycerol lipase and monoacylglycerol lipase.[25] An increase in free fatty acids activates UCP1. Norepinephrine also stimulates glucose uptake into chocolate adipocytes. The duration and intensity of physical exercise are the main factors in stimulating SNS and changing the catecholamine response to physical exercise [24]. Physical exercise has an acute effect of activating UCP1 and stimulating lipolysis. Whereas in a chronic condition, it will stimulate UCP1 gene transcription, mitochondrial biogenesis, BAT hyperplasia, and fat browning. In addition to stimulating the release of norepinephrine from the brain, physical exercise also stimulates the activation of the natriuretic peptide, IL-6, and FGF21 (activated by PGC-1α), which can stimulate the activation of UCP1 in the mitochondria.[19]

This increase in UCP1 expression on WAT indicates that fat browning has occurred. Brown adipocytes are thermogenic cells that are regulated by the sympathetic nervous system (SNS). BAT has characteristics of bright pink to dark due to high vascularity and cytoplasm containing small amounts of fat and mitochondria. High vascularization is needed to supply nutrients and oxygen and also to release heat. This removal of heat through a series of processes called uncoupling processes is regulated by UCP1, a protein in the membrane in the mitochondrial BAT.[8] Increased energy output as heat is what makes weight loss.

Conclusions

Variation of exercise intensity affects level of muscle PGC-1α and the expression of visceral fat's UCP1, which is describing fat browning process in male mice. Moderate-intensity exercise has the highest level of muscle and visceral fat UCP1 expression and will stimulate the increasing of energy expenditure and weight loss.

Declaration of Interest

The authors stated no conflict of interest in this work.

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