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High Intermittent Intensity Training Induces FGF21 Secretion in Obese Rats

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Abstract

The browning of adipose tissue is used as one of possible ways to manage obesity. Physical exercise induces the secretion of myokin fibroblast growth factor 21 (FGF21) as a browning mediator in the adipose tissue. This study aims to determine the effect of high intermittent intensity training (HIIT) induced and continuous moderate intensity training (CMIT) induced FGF21 secretion in skeletal muscle, serum, and adipose tissue. This study involved 18 to 20 week old male Sprague Dawley rats that were divided into four groups: (1) a normal group with the standard diet and HIIT (F1-N); (2) a normal group with the standard diet and CMIT (F2-N); (3) an obese group with high fat diet and HIIT (F1-O); and (4) an obese group with high fat diet and CMIT (F2-O). Our results showed that the HIIT group had higher FGF21 levels than the CMIT group in skeletal muscle and adipose tissue. However, there was no difference between the HIIT group and the CMIT group in serum. Physical exercise with HIIT resulted in a higher level of FGF21 as a browning mediator for obesity treatment.

Keywords: Obesity; Exercise; High intermitten intensity training; FGF21

Introduction

Obesity is one of the world's leding health problems especially in for developed countries. According to World Health Organization (WHO) data, the prevalence of obesity worldwide and its metabolic complications haves nearly doubled since 1980. In 2014 more than 1.9 billion adults 18 years and older were overweight, and of these, over 600 million were obese [1]. One way to manage obesity is by browning white adipose tissue through thermogenesis mediated by physical exercise. Physical exercises cause muscle contraction and sympathetic nerve activation that will activate phosphoinositide 3-kinase (PI3K)/ Akt to regulate fibroblast growth factor 21 (FGF21) [2]. FGF21 is a myokin that plays a role in the browning process [3]. Several studies have reported the alteration of FGF21 levels in serum using various physical exercises varying in intensity, duration and type. Ramos et al. reported that continous moderate intensity training (CMIT) for 2 weeks significantly increased FGF21 [4]. This is in accordance with the recommendation of American College of Sports Medicine (ACSM) for using moderate intensity for obesity resolve [5]. However, other studies show that HIIT can also increase FGF21. Tofighi et al. reported that high intensity intermittent (HIIT) for 8 weeks can improve FGF21 [6]. This suggests that a variation in physical exercise may respond to increase FGF21 levels. Boutcher et al. showed that physical exercise with HIIT can reduce body fat [7]. It is not known how body fat changes are related to the changes in FGF21 levels. Therefore, this study aims to determine the optimal physical exercise formula for increasing FGF21 levels. The change of FGF21 level is also affected by metabolic disorders, including obesity. Obesity leads to an increased level of FGF21 in serum as compensation due to FGF21 resistance in adipose tissue [8]. Therefore, this study aims to determine the effects of HIIT and CMIT on FGF21 levels in obesity.

Materials and Methods

Study and design

This is an in vivo study using 16 Sprague Dawley rats that were 8 to 10 weeks old and weighed 90 to 190 g. The rats were purchased from the V-Stem Bogor, Indonesia. Before and during the treatment, the health of the rats was maintained. Rats were fed and given water ad libitum. The cage was kept clean and the animal had 12 hours cycless of light and darkness. This study was approved by the ethics committee of the Medical Faculty University of Indonesia.

Animal group assignment

At the beginning of the experiment, the rats were randomly assigned into two groups (n = 8 per group): as follows: (1) the normal group received a standard diet (6% fat); (2) the obese group received a high-fat diet (19.09% fat). After 10 weeks on the diet, the rats were categorized as obese when the Lee index was greater than 310 (Data not shown). Furthermore, rats were randomly assigned into four groups (n=4 per group), as follows: (1) a normal group with standard diet (6%) and HIIT (F1-N); (2) a normal group with a standard diet (6%) and CMIT (F2-N); (3) an obese group with a high fat diet (19,09%) and HIIT (F1-O); and (4) an obese group with a high fat diet (19,09%) and CMIT (F2-O).

Physical exercise protocols

Physical exercise was given to normal and obese rats 5 days a week for 8 weeks. Before the rats performed the physical exercise, they adapted for a week to minimize the potential stress. This study used two types of physical exercise, as follows.

High Intermitten Intensity Training (HIIT): HIIT was adopted from Jamali et al. An animal treadmill with a speed of 29 m/min was used along with 1-minute active rest intervals. The active rest was the continuation of running on the treadmill, but a pace of 13 m/min. Each practice session started with five repetitions of 30 seconds. The duration and speed increased gradually every week. In addition, this protocol included warm up and cool down at a speed of 10 m/min for 5 minutes [9].

Continuous Moderate Intensity Training (CMIT): CMIT was adopted from Shin et al. Rats of the training groups underwent exercise

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training on an animal treadmill. For the first week, the exercise intensity consisted of 5 m/min for 5 minutes, 12 m/min for 5 minutes and 18 m/min for 20 minutes. In the last 4 weeks, the exercise intensity was increased to 10 m/min for 5 minutes, 16 m/min for 5 minutes, and 22 m/min for 30 minutes [10].

Sampling

The serum and tissue were collected from the animals after 48 hours of physical exercise and 12 hours of fasting. Before decapitation, the rats were given total anesthesia by intraperitoneal injection using a combination of 0.01 mL/kg of xylazine hydrochloride and ketamine 0.05 mL/kg. Serum was taken through retro-orbitally, and then centrifuged for 10 minutes at 3000 rpm and stored at -80°C before analysis. In addition, skeletal muscle (gastrocnemius) and white adipose tissue were homogenized. Subsequently, the supernatant was transferred into 1.5 mL microtubes and immediately stored at -80°C before analysis. The FGF21 was measured by using enzyme linked immunosorbent assay (ELISA) (MF2100 R & D System) [11].

Statistical Analysis

The normality of distribution was checked with the Shapiro–Wilk test. All measurement data are expressed as mean ± standard error mean (SEM) and analysed by two-way analysis of variance (ANOVA). A *P* value <0.05 was considered statistically significant. All statistical analyses were performed using statistical software SPSS version 20.0.

Results and Discussion

Body weight measurements

There was no significant difference in body weight in the HIIT and CMIT groups. Further, the HIIT group was more effective in maintaining body weight than the CMIT group (Figure 1).

FGF21 levels in skeletal muscle and training exercise

The FGF21 levels in the obese group did not differ from the normal group. This finding shows that obesity has no effect on FGF21 levels in skeletal muscle. However, the changes of FGF21 levels in skeletal muscle are more affected by physical exercise factors than by diets. This study shows that HIIT is more effective than CMIT in increasing FGF21 levels in skeletal muscle. However, no FGF21 changes were found in skeletal muscle due to diet (Figure 2).

FGF21 serum levels and training exercise

Physical exercise and high-fat diet did not affect serum FGF21 levels. There were no significant differences in FGF 21 serum levels in serum of the obese and normal rats (p>0.05). In addition, there was no significant difference between HIIT and CMIT (p>0.05). Serum FGF21 levels are always maintained in stable state adapted to physical exercise and dietary (Figure 3).

FGF21 levels in white adipose tissue and training exercise

FGF21 levels in white adipose tissue was higher in the obese group than in the normal group. The increase of FGF21 occurs because of both physical exercise and diet factors. However, we found that HIIT is more effective than CMIT in increasing FGF21 in white adipose tissue (Figure 4).

Discussion

This study showed HIIT is more effective than CMIT for increasing FGF21 levels in skeletal muscle. Thus, the increase in FGF21 levels in skeletal muscle is due to differences of duration, intensity, and type of physical exercises. The increase of FGF21 in skeletal muscle is due to the activation of the sympathetic nervous system to release norepinephrine [3,4]. A high intensity physical exercise can induce higher sympathetic nervous system responses than moderate intensity physical exercise. In addition, physical exercise will activate Akt signalling which plays an important role in cellular responses such as FGF21 regulation induced by muscle contraction [12,13]. A study by Sakamoto et al. showed that high and moderate intensity physical exercise had an effect on the increased Akt signalling of rat skeletal muscle contraction [13]. However, the muscle contraction activating PI3K/Akt corresponds to the intensity, duration and type of physical exercise.

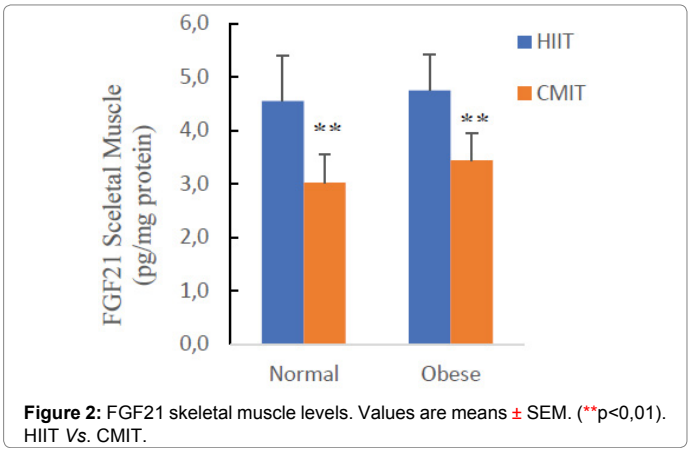

Figure 2: FGF21 skeletal muscle levels. Values are means ± SEM. (**p<0,01). HIIT *Vs*. CMIT.

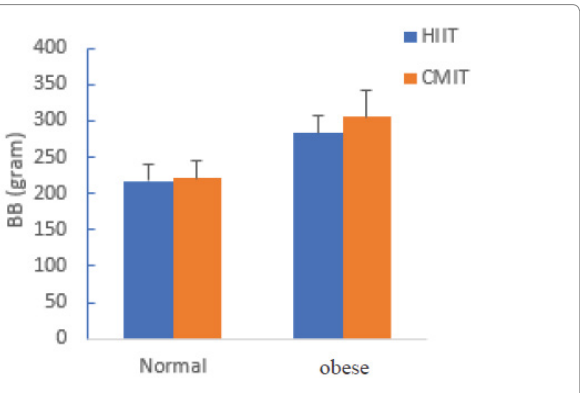

Figure 1: The body weight of normal and obesity group treated with HIIT and CMIT. Values are means ± SEM. (P>0,05).

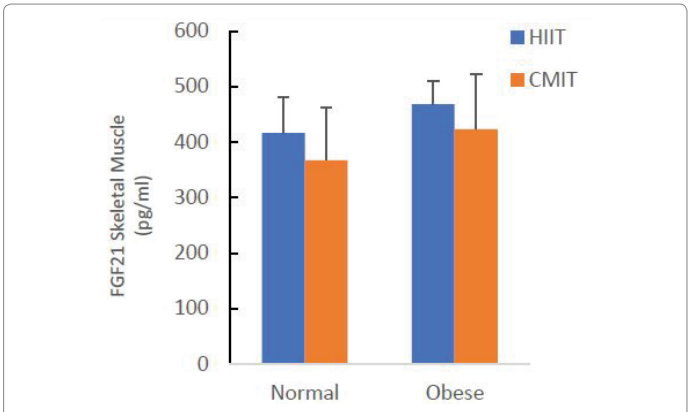

Figure 3: FGF21 Serum levels. Values are means ± SEM (p>0,05).

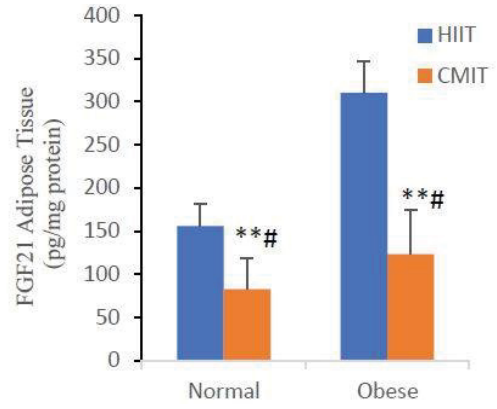

Figure 4: FGF21 adipos tissue levels. Values are means ± SEM. (**p<0. 01): Formula 1 *Vs*. Formula 2; (#p<0,05) Diet Standard *Vs*. High Fat Diet.

This study found no difference in the FGF21 levels in the normal and obese condition. This suggests that the state of obesity given physical exercise does not occur FGF21 resistance. As is known, according to Diaz et al. the state of obesity will lead to FGF21 reliance demonstrated by elevated levels of abnormal FGF 21 in serum [14]. This is due to the proinflammation that occurs in obesity conditions that would interfere with Klotho β expression in adipose tissue, leadings to FGF21 resistance [15]. FGF21 binds to FGFr1c receptors and klotho β co-receptors on the surface of the white adipose tissue membrane [16]. This finding is supported by Nygard et al., who reported that obese monkeys showed a decrease in Klotho β expression in adipose tissue resulting in FGF21 resistance [17].

FGF 21 resistance could be prevented by both HIIT and CMIT physical exercise. A study by Katze (2017) shows that physical exercise in obesity increases FGFr1c [18]. Increased FGFR1c will compensate with a decrease in Klotho β expression in white adipose tissue, which increases FGF21 action in obesity [18]. Although this study did not measure FGFr1c, increased FGFr1c will increase FGF21 bound in adipose tissue. This study showed increased FGF21 levels in white adipose tissue.

We found that HIIT is more effective increasing FGF21 in white adipose compared with CMIT, according to FGF21 level in skeletal muscle. Our findings are consistent with research by Kruse et al. which showed that FGF21 secreted by skeletal muscle will increase FGF21 levels in white adipose tissue [19]. FGF21 secreted by skeletal muscle binds to receptors in white adipose tissue. Thus, HIIT is more effective increasing FGF21 secretion in skeletal muscle that will bind to receptors in white adipose tissue [20]. FGF21 binds with FGFR1c receptor, activating signalling that induces browning through the activation of SIRT1, which causes deacetylation of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) will induce uncoupling protein 1 (UCP-1) expression. UCP-1 subsequently generates heat by uncoupling oxidative phosphorylation resulting in a beneficial body energy expenditure in decreasing excess energy in the body that affects weight loss [8,21,22].

Conclusion

Physical exercise using HIIT is better in increasing FGF21 skeletal muscle levels so that it will increase FGF 21 levels, so that it will increase FGF21 levels in white adipose tissue. Increased FGF 21 will play a role in the process of browning adipose tissue, handling benefit for reducing obesity.

Acknowledgment

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