Moderate intensity exercise decreases the circulating level of betatrophin and its correlation among markers of obesity in women

by Purwo Sri Rejeki
Purwo Sri Rejeki*, Pradika Gita Baskara, Lilik Herawati, Adi Pranoto, Hayuris Kinandita Setiawan, Ronny Lesmana and Shariff Halim

Moderate-intensity exercise decreases the circulating level of betatrophin and its correlation among markers of obesity in women

https://doi.org/10.1515/jbcpp-2021-0393
Received December 22, 2021; accepted February 15, 2022; published online March 15, 2022

Abstract

Objectives: Positive energy homeostasis due to overnutrition and a sedentary lifestyle triggers obesity. Obesity has a close relationship with elevated levels of betatrophin and may increase the risk of developing metabolic syndrome. Therefore, lifestyle modification through a non-pharmacological approach based on physical exercise is the right strategy in lowering betatrophin levels. This study aimed to analyze the effect of moderate-intensity interval and continuous exercises on decreased betatrophin levels and the association between betatrophin levels and obesity markers in women.

Methods: A total of 30 women aged 20–24 years old were randomly divided into three groups. Measurement of betatrophin levels using Enzyme-Linked Immunosorbent Assay (ELISA). Data analysis techniques used were one-way ANOVA and parametric linear correlation.

Results: The results showed that the average levels of betatrophin pre-exercise were 200.40 ± 11.03 pg/mL at CON, 203.07 ± 42.48 pg/mL at MIE, 196.62 ± 21.29 pg/mL at MCE, and p=0.978. Average levels of betatrophin post-exercise were 226.65 ± 18.96 pg/mL at CON, 109.31 ± 11.23 pg/mL at MIE, 52.38 ± 8.18 pg/mL at MCE, and p=0.000. Pre-exercise betatrophin levels were positively correlated with age, BMI, FM, WHR, FBG, and PBF (p<0.001).

Conclusions: Our study showed that betatrophin levels are decreased by 10 min post-MIE and post-MCE. However, moderate-intensity continuous exercise is more effective in lowering betatrophin levels than moderate-intensity interval exercise. In addition, pre-exercise betatrophin levels also have a positive correlation with obesity markers.

Keywords: betatrophin; moderate-intensity exercise; myokine; obesity.

Introduction

Obesity is a metabolic disease that is the third leading cause of death and has become a global epidemic [1, 2]. Obesity is already considered an epidemic and has now become a pandemic [3]. This is due to the prevalence rate of obesity experiencing a continuous increase in both developed countries and developing countries [1, 4]. It was estimated that 1.9 billion people over the age of 18 were overweight, and 650 million of who were obese comprising 11% of men and 15% of women [5], meaning that more than one-third of adults globally were obese [6]. If every year, the prevalence of obesity continues to increase, it is estimated that by 2025, the prevalence of obesity will be 18% of men and 21% of women [7]. Based on Basic Health Research (Risksdas) in 2018 showed that the prevalence of obesity in Indonesia people aged over 18 years old had increased, which was 21.8%, the number was higher than in 2013 (14.8%) and in 2007 (10.5%) [8]. Meanwhile, the prevalence of obesity in children in recent decades has also increased worldwide [9, 10]. In 2016 estimated that the prevalence of obesity in the world in children and adolescents aged 5–19 years is 124 million people and 213 million people are overweight [11]. Based on previous data, it was also reported that most of the adolescents worldwide have low levels of physical activity [12]. Physiologically, changes in lifestyle behavior, such as increased time sitting, lying down [13], and reduced desire to exercise are
the causes of increased body weight and risk of obesity [14, 15].

Obesity increases the risk of developing metabolic syndrome, as obesity is associated with increased levels of total cholesterol, increased triglyceride and low-density lipoprotein (LDL) levels, and decreased levels of high-density lipoprotein (HDL) [16], so that obese individuals are susceptible to type 2 diabetes mellitus [17], hypertension [18], hypercholesterolemia [19], several types of cancer [20, 21], nonalcoholic fatty liver disease (NAFLD), and dyslipidemia [22]. In addition, obesity also causes the heart workload to increase, thus increasing the risk of cardiovascular disease [23, 24]. In the condition of obesity, there is also impaired insulin secretion by pancreatic β-cells caused by increased levels of betatrophin [25–28]. Elevated levels of betatrophin can also have an effect on the kidneys and female organs, resulting in kidney problems [29] and polycystic ovarian syndrome (PCOS) [30]. Excessive levels of betatrophin can also inhibit the performance of the lipoprotein lipase (LPL) enzymes [31, 32]. The stunted performance of LPL enzymes causes fat to be irreversible into an energy source [33], resulting in increased fat storage in adipocytes [34]. Increased fat storage in adipocytes is one of the causes of obesity [35, 36]. Therefore, the discovery of new solutions for obesity prevention is becoming a very important target to do and potential therapies with high feasibility at a low cost for obesity prevention in the global community are urgently needed.

Over the past decade, several interventions have been made on how to tackle obesity and boost metabolism without increasing the activity of internal stressors in the body [37, 38]. Recent findings suggest that exercise may lower betatrophin levels in obese people [26, 27]. Physical activity is organized in exercise programs oriented to strength development, low-intensity fitness, or a combination of these two [39]. The design of a program must follow specific rules with regard to the exercise to be undertaken, as well as its intensity, duration, and frequency, in order to obtain benefits [39]. A research conducted by Abu Fahla et al. [26] reported that the combination of both moderate-intensity aerobic (30 min) and resistance exercises using either a treadmill or cycling (10 min) lowered betatrophin levels in obesity. Likewise, the study of Susanto et al. [37] proved that moderate-intensity exercise lowered betatrophin levels in nonprofessional athletes. However, a research conducted by Enteshary et al. [40] found different results in which betatrophin levels increased post-moderate-intensity exercise in women with Type 2 Diabetes (T2D). Thus, the fundamental impact of moderate-intensity exercise on decreasing betatrophin levels remains controversial. Therefore, the aim of the present paper was to elaborate the potential regulation of moderate-intensity exercise decreases the circulating level of betatrophin and its correlation among markers of obesity in women.

Materials and methods

Experimental design

This research is a real experiment with a research design of randomized pretest–posttest control group design. The total subjects participating in the study were 30 women aged 21.27 ± 0.25 years old with body mass index (BMI) of 28.82 ± 0.30 kg/m², blood pressure (systolic blood pressure 113.33 ± 1.30 mmHg, diastolic blood pressure 76.00 ± 1.23 mmHg), resting heart rate (RHR) of 75.57 ± 2.33 bpm, fasting blood glucose (FBG) of 90.23 ± 1.33 mg/dL, hemoglobin (Hb) of 14.99 ± 0.26 g/dL, and maximum oxygen volume (VO2max) of 28.08 ± 0.66 mL/kg/min examined using aastrad 6 min cycle test method. All subjects were examined both physically and psychologically. All subjects obtained information orally or in writing about the research. The subjects filled out and signed informed consent before participating in the research. All of our research procedures comply with the Declaration of the World Medical Association of Helsinki regarding the ethical conduct of research involving human subjects.

Exercise protocol

The exercise program was applied and supervised by professional officers from the Fitness Center of Malang Health Office. The subjects were randomly divided into three groups: CON (n=10, control without intervention), MIE (n=10, moderate-intensity interval exercise), and MCE (n=10, moderate-intensity continuous exercise). The MIE intervention was carried out by employing the subjects running on a treadmill with moderate intensity of 60–70% HRmax for 45 min with details of 5 min of warming up (50–60% HRmax), 35 min of core exercise (5 min of work (60–70% HRmax) interspersed with active recovery on the treadmill for 25 min (60–60% HRmax) performed 5 times a while, and 5 min of cooling (50–60% HRmax) [41–44]. The intervention was conducted at 07.00–09.00 am [45, 46] using a treadmill (Pulsar 6.0 HP Cosmos Sports & Medical, Nussdorf-Traunstein, Germany) [47]. Heart rate monitoring during exercise used a polar heart rate monitor (Polar H7 Heart Rate Sensor, Inc., USA). The research environment had a room temperature of 26 ± 1 °C and a room humidity level of 50–70% [48, 49].

Blood samples

Blood samples were collected from a 4 mL cubital vein after a 12 h overnight fasting [50, 51]. At the time of the blood draw, the subjects were in a lying position. Blood samples were taken at 30 min pre-exercise, and 10 min post-exercise. At the time of pre-exercise and post-exercise blood draws, the subjects remained in a fasting condition but they were allowed to drink mineral water without calories to prevent dehydration. The blood was centrifuged for 15 min at a speed of 3,000 rpm. The serum was then separated and stored at −80 °C for analysis of betatrophin levels on the next day [51–53].
Blood analysis

Examination of betatrophin levels was conducted at the Laboratory of Physiology of the Faculty of Medicine, Universitas Brawijaya, Malang, using the enzyme-linked immunosorbent assay (ELISA) kit (Cat No. E116644a; ELab Science Co., Wuhan) with a standard curve range of 78–5,000 pg/mL and betatrophin sensitivity levels in a kit of 32 pg/mL.

FBG examination was carried out using Accu-Chek Performa (Roche, Mannheim, Germany) with mg/dL concentration unit, while Hb examination used Easy Touch (Easy Touch, Heinchu, Taiwan) with g/dL concentration unit.

Anthropometric measurements and physical fitness

Body height measurements were conducted using a stadiometer (SECA, Chino, CA, USA). Measurements of obesity markers included body weight, body mass index (BMI), body fat percentage (BFP), and fat mass (FM) using TANITA Body Composition Analyzer BC-601W (TANITA Corporation of America Inc, Arlington Heights, IL, USA). Measurement of the waist to hip ratio (WHR) was conducted by calculating waist circumference (WC) divided by hip circumference (HC). Measurement of maximal oxygen volume (VO2max) by the Astrand 6 min cycle test method was performed using a Monark 828 E Version 1010 ergo cycle (Monark, Vansbro, Sweden). Measurement of resting heart rate (RHR) was conducted using Beurer Pulse Oximeter (BO 30 Pulse Oximeter, Beurer North America LP, Hallandale Beach, FL, USA). Blood pressure was measured using an automated device (OMRON (OMRON Model HEM-7130 L, Omron Co., Onalda, Japan) at the non-dominant arm 3 times consecutively with a 1–2 min interval between two measurements while the participants were in a seated position.

Statistical analysis

Statistical analysis was conducted using SPSS software version 17 (SPSS Inc., Chicago, IL, USA). The normality test was conducted using the Shapiro–Wilk test, while the homogeneity test used the Levene test. Different tests were conducted using paired sample T-Test, one-way ANOVA, and then followed by Tukey’s honestly significant difference (HSD) post hoc test and linear correlation with Pearson product-moment model. Data were presented as the mean ± standard error of the mean (SEM). Significant will be considered with p value ≤ 0.05.

Results

The basic profiles of the samples are displayed in Table 1. Table 1 shows that the average characteristic data of the study subjects showed no significant differences in all parameters of each group (p ≤ 0.05). The results of the analysis of betatrophin levels between pre-exercise and post-exercise in each group are presented in Figure 1.

Figure 1 shows that betatrophin levels between pre-exercise and post-exercise in the CON group had no change and tended to be the same, while in the MIE and MCE groups, there was a change and the betatrophin levels tended to decrease. Paired sample T-Test results in the CON group showed that there was no significant difference in average betatrophin levels between pre-exercise and post-exercise (200.40 ± 11.03 vs. 226.65 ± 18.96 pg/mL, (p-value=0.269)) (Figure 1). However, the MIE group showed significant differences in average betatrophin levels between pre-exercise and post-exercise (203.08 ± 42.48 vs. 109.31 ± 11.23 pg/mL, (p-value=0.046)) (Figure 1). Likewise, the MCE group showed significant differences in average levels of betatrophin between pre-exercise and post-exercise (196.62 ± 21.29 vs. 52.38 ± 8.18 pg/mL, (p-value=0.000)) (Figure 1). The results

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group</th>
<th>One-way ANOVA p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs.</td>
<td>CON (n=10)</td>
<td>MIE (n=10)</td>
</tr>
<tr>
<td></td>
<td>21.30 ± 0.30</td>
<td>21.50 ± 0.64</td>
</tr>
<tr>
<td>Body height, m</td>
<td>1.57 ± 0.01</td>
<td>1.59 ± 0.02</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>73.30 ± 1.80</td>
<td>73.33 ± 2.93</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29.42 ± 0.40</td>
<td>28.81 ± 0.70</td>
</tr>
<tr>
<td>BFP (%)</td>
<td>45.17 ± 1.14</td>
<td>42.40 ± 1.43</td>
</tr>
<tr>
<td>FM, kg</td>
<td>35.66 ± 1.36</td>
<td>34.32 ± 2.49</td>
</tr>
<tr>
<td>WHR</td>
<td>0.81 ± 0.01</td>
<td>0.81 ± 0.01</td>
</tr>
<tr>
<td>Hb, g/dL</td>
<td>15.05 ± 0.57</td>
<td>14.97 ± 0.29</td>
</tr>
<tr>
<td>FBG, mg/dL</td>
<td>91.90 ± 1.82</td>
<td>90.50 ± 2.69</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>115.00 ± 2.69</td>
<td>111.00 ± 1.79</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>78.00 ± 2.00</td>
<td>73.00 ± 2.13</td>
</tr>
<tr>
<td>RHR, bpm</td>
<td>73.70 ± 3.73</td>
<td>77.30 ± 4.92</td>
</tr>
<tr>
<td>VO2max, mL/kg/min</td>
<td>27.40 ± 0.61</td>
<td>27.59 ± 1.39</td>
</tr>
</tbody>
</table>

BMI, Body mass index; BFP, Percentage of body fat; FM, Fat mass; WHR, Waist to hip ratio; Hb, Hemoglobin; FBG, Fasting blood glucose; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; RHR, Resting heart rate; VO2max, Maximum oxygen volume; CON, Control group; MIE, Moderate-intensity interval exercise group; MCE, Moderate-intensity continuous exercise group. One way-ANOVA. Data are presented as mean ± SEM.
Table 2 of the One-way-ANOVA test results shows that there was no significant difference in average betatrophin levels based on the timing of pre-exercise blood collection in each group (p>0.05), while in post-exercise and delta (Δ) (Post–Pre), the results showed significant differences in average levels of betatrophin (p<0.001). Tukey's HSD post hoc test results showed that there was a significant difference in average levels of post-exercise betatrophin between MIE and CON (p<0.001), MCE and CON (p<0.001), and MCE and MIE (p<0.05). Likewise, delta (Δ) (Post–Pre) showed significant differences in average levels of betatrophin between MIE and CON (p<0.05) and MCE and CON (p<0.001), while MCE and MIE showed no significant difference (p>0.05).

The results of the correlation of pre-exercise betatrophin levels with obesity markers and characteristic parameters of the study subjects are shown in Figure 2.

Preliminary research results found a significant association of pre-exercise betatrophin levels with obesity markers and the characteristic parameters of study subjects including age and FBG. Pearson product-moment linear correlation parametric analysis showed that pre-exercise betatrophin levels were positively correlated with age (r=0.557, p<0.05), BMI (r=0.660, p<0.001), FM (r=0.385, p<0.05), WHR (r=0.543, p<0.05), FBG (r=0.536, p<0.05), and PBF (r=0.698, p<0.001).

Table 2: Betatrophin levels in each group based on the time of blood collection.

<table>
<thead>
<tr>
<th>Time</th>
<th>Betatrophin, pg/mL</th>
<th>One Way-ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CON (n=10)</td>
<td>MIE (n=10)</td>
</tr>
<tr>
<td>Pre-exercise</td>
<td>200.40 ± 11.03</td>
<td>203.07 ± 42.48</td>
</tr>
<tr>
<td>Post-exercise</td>
<td>226.65 ± 18.96</td>
<td>109.31 ± 11.23</td>
</tr>
<tr>
<td>Delta (Δ) post–Pre</td>
<td>26.25 ± 22.31</td>
<td>-93.76 ± 40.64</td>
</tr>
</tbody>
</table>

One way-ANOVA, followed by Tukey's HSD post hoc test, was used to compare the differences among groups. Data are presented as mean ± SEM. *Significant vs. control group (CON) (p<0.001). **Significant vs. moderate-intensity interval exercise group (MIE) (p<0.05).
Therefore, we evaluated the effects of moderate-intensity interval exercise and moderate-intensity continuous exercise on decreasing betatrophin levels in obese women.

Our study demonstrated that there was no difference in betatrophin levels between pre-exercise vs. post-exercise on CON, while MIE and MIC showed significant differences in betatrophin levels between pre-exercise and post-exercise (Figure 1). The results were in line with the results of a study by Abu-Farha et al. [26] reporting that a combination of moderate-intensity aerobic exercise (30 min) and endurance exercise using a treadmill or cycling (10 min) significantly lowered betatrophin levels in obese subjects. Likewise, a research by Susanto et al. [37] reported that moderate-intensity exercise significantly lowered betatrophin levels in non-professional athlete subjects. The decrease in betatrophin levels is likely due to intervention factors (MIE and
MICE). At the time of intervention, there is an increase in the need for energy obtained from blood glucose, thus causing blood glucose levels to decrease. A research by Zheng et al. [56] reported that moderate-intensity aerobic exercise lowered blood glucose levels and improved glycemic control. Likewise, a study by van Dijk et al. [57] using obese subjects who were given moderate-intensity acute exercise interventions concluded that moderate-intensity acute exercise significantly lowered blood glucose levels. Decreased blood glucose levels can cause betatrophin secretion to decrease [58]. Zhang [59] reported that high blood glucose levels in obesity increase betatrophin secretion in the liver. Gasarova et al. [60] revealed that glycemic control in addition to avoiding hypoglycemia and hyperglycemia could also decrease excessive betatrophin expression.

Obesity is a condition where there is an excessive accumulation of body fat [21]. Excess fat in the body leads to increased triglyceride levels (hypertriglyceridemia) [28]. Increase in triglyceride levels could stimulate betatrophin levels, so that obese individuals experience an increase in betatrophin levels [26, 27]. Elevated levels of betatrophin can inhibit the performance of the lipoprotein lipase (LPL) enzymes [31, 32, 59]. Inhibition of LPL enzymes makes triglycerides difficult to convert into energy [33]. In addition to having high levels of betatrophin, obese people also have high blood glucose levels [27, 61]. Meanwhile, the administration of acute exercise intervention with moderate-intensity requires glucose (glucose uptake) to be converted into energy (ATP) from carbohydrates, fats, and proteins [62]. Increased glucose uptake to be converted into energy makes glucose levels in the blood and betatrophin secretion decrease [58], so that acute exercise with moderate intensity can respond to the decrease in betatrophin levels in the body faster [26, 27].

The literature states that exercise can be used as a useful tool for the prevention, treatment, and rehabilitation of several diseases, such as diabetes mellitus and cardiovascular disease [39]. In diabetic patients exercise can be recommended and prescribed to manage blood glucose and improve the quality of general good health [13]. However, this recommendation must also take into account the lifestyle and habits of diabetics, so DM treatment should be carried out by a multidisciplinary team specializing in pharmacological aspects and physical exercise to increase the effectiveness of therapy [13]. In addition, an exercise that is prescribed and performed properly and correctly has also been shown to be safe and effective for people with cardiovascular disease [39].

Betatrophin is a newly discovered adipocytokine and is believed to play an important role in the body’s metabolism [54]. Betatrophin is one of the main focuses in obesity research and relevant research results have been published continuously [26, 63]. Several epidemiological studies have shown that there is an independent relationship between circulating betatrophin levels and obesity [64-66], while other studies reported no association [63, 67-69]. Inconsistently results are likely due to too few subject counts and also influenced by many factors [54]. Therefore, we conducted a re-study to further evaluate the relationship between circulating betatrophin levels and obesity.

Our data present that betatrophin levels have a positive relationship with age, body mass index (BMI), fat mass (FM), waist-to-hip ratio (WHR), percentage of body fat (PBF), and fasting blood glucose (FBG) (Figure 2). The results confirm previous findings that reported that betatrophin levels were positively correlated with age, BMI, PBF [26, 33, 61, 70-72], WHR [34], FM [65], and percentage of body fat (FAT %) [70]. This association is likely due to an increase in obese individuals with elevated levels of betatrophin [27, 28, 63, 64, 67]. It is as evidenced by the results of a meta-analysis conducted by Ye et al. [54] which reported that betatrophin levels were higher in obese individuals compared to those in healthy individuals. Elevated levels of betatrophin can inhibit the performance of the LPL enzymes [31, 32]. The stunted performance of LPL enzymes causes fat to be irreversible into an energy source [70], resulting in increased fat storage in adipocytes [34].

Adipose tissue, known as an important endocrine organ, has attracted a lot of attention because it has many effects on several metabolic processes, such as glucose homeostasis, lipid metabolism, inflammation, and blood pressure [54]. Betatrophin is known as angiotropin-like protein 8 (ANGPTL8), refeeding induced fat and liver (RIFL), chromosome 19 open reading frame 80 (C19orf80), hepatocellular carcinoma-associated protein TD26, and lipasin, which is a new adipolgue secreted from adipose and liver tissue [55]. Previous studies using mouse models implied an important role of betatrophin in some metabolic-related pathways, such as lipid metabolism and energy balance [26]. Based on a meta-analysis of 9 observational studies, individuals with obesity have higher levels of betatrophin than normal-weight individuals [54]. There is emerging evidence supporting a positive association between betatrophin levels and obesity [26, 54, 65, 66]. In vitro studies conducted by Ren et al. [73] showed that betatrophin expression increased more than 100-fold during cell adipogenesis 3T3-L1. Its knockout in 3T3-L1 cells during adipogenesis and its knockdown lead to a decrease in adipogenesis. Furthermore, betatrophin expression increased about 8 times in white adipose tissue (WAT) in obese model mice compared
to wild mice [74]. Likewise, betatrophin mRNA is expressed very highly in humans with obesity [26]. High concentrations of betatrophin in circulation can directly increase the risk of obesity in adults [54]. Therefore, betatrophin can serve as a viable therapeutic target in the fight against obesity in adults.

There are some limitations to this study. First, the number of subjects who participated in this study was still relatively small who met the inclusion criteria and participated in the training program. Thus, a large number of samples may be needed to further analyze the effect of moderate-intensity exercise on the modulation of betatrophin levels in obese women. Second, the type of exercise intervention for this study is a single intervention (acute exercise), several possible types and intensity of exercise can affect the regulation of betatrophin. Therefore, further research is needed on the type and intensity of exercise. Third, circulating betatrophin levels can be influenced by gender and lipid profile, so further research can add to the examination of body fat profiles, such as total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and comparing betatrophin levels between men and women.

Conclusions

Taken together, the results of this study showed that moderate-intensity interval exercise and moderate-intensity continuous exercise performed for 30–35 min lowered betatrophin levels. However, moderate-intensity continuous exercise is more effective in lowering betatrophin levels compared to moderate-intensity interval exercise. Therefore, moderate-intensity continuous exercise can be a major modality in lowering betatrophin levels and betatrophin can serve as a promising therapeutic target for obesity in adults. Further research is needed to explore in more detail the physiological mechanisms of exercise in lowering betatrophin levels in obesity.

Acknowledgments: We would like to express our gratitude to the Faculty of Sport Science, State University of Malang that has provided facilities in the screening process of a prospective research subject and the Fitness Center of Health Ministry of Malang that has provided facilities well. Also, we greatly appreciate and wish to thank Pola Atlet Indonesia (PUI) Blood Transfusion Unit (UTD) of Malang that has assisted the blood sampling and blood centrifuge processes. This includes but is not limited to all parties of Physiology Laboratory, Faculty of Medicine, Universitas Brawijaya Malang who have helped the analysis process of betatrophin levels and all volunteers who have participated in this study.

Research funding: This study is supported by the Fundamental Research Program of the Ministry of Research, Technology and Higher Education, Indonesia, under Grant Number: 4/A/MD/BI/KP.PTBH/2020 and 580/UN3.14/PT/2020.

Author contribution: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: Authors state no conflict of interest.

Informed consent: Informed consent was obtained from all individuals included in this study.

Ethical approval: Based on the ethical standards of the Declaration of Helsinki 1975, this study has been approved by the Health Research Ethics Commission of the Faculty of Medicine, Universitas Airlangga, Surabaya with registration number: 309/EC/KEPK/FRU/A/2019.

References


Moderate intensity exercise decreases the circulating level of betatrophin and its correlation among markers of obesity in women

**Originality Report**

<table>
<thead>
<tr>
<th>Similarity Index</th>
<th>Internet Sources</th>
<th>Publications</th>
<th>Student Papers</th>
</tr>
</thead>
<tbody>
<tr>
<td>20%</td>
<td>15%</td>
<td>18%</td>
<td>0%</td>
</tr>
</tbody>
</table>

**Primary Sources**


2. Robert G. Hahn, Marc Giménez-Milà. "The intracellular fluid compartment is smaller than commonly believed when measured by whole-body bioimpedance", Journal of Basic and Clinical Physiology and Pharmacology, 2021

3. Petros C. Dinas, Ian M. Lahart, James A. Timmons, Per-Arne Svensson, Yiannis Koutedakis, Andreas D. Flouris, George S. Metsios. "Effects of physical activity on the link between PGC-1a and FNDC5 in muscle, circulating Irisin and UCP1 of white adipocytes"
<table>
<thead>
<tr>
<th>No.</th>
<th>Title</th>
<th>Authors and Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>High betatrophin in coronary patients protects from cardiovascular events</td>
<td>Andreas Leiherer, Janine Ebner, Axel Muendlein, Eva M. Brandtner et al.</td>
</tr>
<tr>
<td>5</td>
<td>Interleukin-15 and creatine kinase response to high-intensity intermittent exercise training</td>
<td>Thaislaine dos Santos, Fabio Santos Lira, Barbara Moura Antunes</td>
</tr>
<tr>
<td>6</td>
<td>Levels of lipoprotein and homocysteine in non-obese and obese patients with polycystic ovary syndrome</td>
<td>Murat Yilmaz, Aydan Bi'ri, Neslihan Bukan, Ayhan Karakoç, Banu Sancak, Füsun Törüner, Hatice Paşaoğlu</td>
</tr>
<tr>
<td>8</td>
<td>Serum Concentrations of Betatrophin and Its Association with Indirect Indices of Insulin</td>
<td>Agnieszka Adamska, Agnieszka Łebkowska, Małgorzata Jacewicz, Anna Krentowska et al.</td>
</tr>
</tbody>
</table>
Publication

Fangfang Xu, Dandan Tian, Xiaoyang Shi, Kai Sun, Yuqing Chen. "Analysis of the Expression and Prognostic Potential of a Novel Metabolic Regulator ANGPTL8/Betatrophin in Human Cancers", Pathology and Oncology Research, 2021
Publication

journals.plos.org
Internet Source

researchspace.auckland.ac.nz
Internet Source

f1000researchdata.s3.amazonaws.com
Internet Source

themedicalacademy.in
Internet Source

www.grafiati.com
Internet Source

www.rssdi.in
Internet Source

Crujeiras, A B, M A Zulet, I Abete, M Amil, M C Carreira, J A Martínez, and F F Casanueva. "Interplay of atherogenic factors, protein
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>bmcendocrdisord.biomedcentral.com Internet Source</td>
</tr>
<tr>
<td>digilib2.unisayogya.ac.id Internet Source</td>
</tr>
<tr>
<td>&quot;Annual Conference of the British Association of Sport and Exercise Sciences&quot;, Journal of</td>
</tr>
</tbody>
</table>
Alessandro Ciresi, Giuseppe Pizzolanti, Valentina Guarnotta, Carla Giordano. "Circulating irisin levels in children with growth hormone (GH) deficiency before and after 1 year of GH treatment", The Journal of Clinical Endocrinology & Metabolism, 2018


docplayer.biz.tr

onlinelibrary.wiley.com

rgu-repository.worktribe.com

rimi.imi.bg.ac.rs

www.frontiersin.org


of Obese Patients’ Blood Plasma",
International Journal of Molecular Sciences, 2020

Publication

Bert Bond, Craig A. Williams, Carly Isic, Sarah R. Jackman, Keith Tolfrey, Laura A. Barrett, Alan R. Barker. "Exercise intensity and postprandial health outcomes in adolescents",
European Journal of Applied Physiology, 2014

Publication

Elizabeth Waters, Rosie Ashbolt, Lisa Gibbs, Michael Booth et al. "Double disadvantage: the influence of ethnicity over socioeconomic position on childhood overweight and obesity: findings from an inner urban population of


Mahtab Enteshary, Fahimeh Esfarjani, Jalil Reisi. "Comparison of the Effects of Two Different Intensities of Combined Training on Irisin, Betatrophin, and Insulin Levels in Women with Type 2 Diabetes", Asian Journal of Sports Medicine, 2019


Martina Tomić, Romano Vrabec, Sania Vidas Pauk, Tomislav Bulum, Spomenka Ljubić. "Systemic inflammation and dyslipidemia are associated with retinopathy in type 2 but not in type 1 diabetes", Scandinavian Journal of Clinical and Laboratory Investigation, 2020
<table>
<thead>
<tr>
<th></th>
<th>Yani Ke, Shan Liu, Zheyuan Zhang, Jie Hu. &quot;Circulating angiopoietin-like proteins in metabolic-associated fatty liver disease: a systematic review and meta-analysis&quot;, Lipids in Health and Disease, 2021</th>
</tr>
</thead>
<tbody>
<tr>
<td>46</td>
<td></td>
</tr>
<tr>
<td>47</td>
<td>ir.lib.uth.gr</td>
</tr>
<tr>
<td>48</td>
<td>journalofnaturalproducts.com</td>
</tr>
<tr>
<td>49</td>
<td>koreascience.kr</td>
</tr>
<tr>
<td>50</td>
<td><a href="http://www.int-res.com">www.int-res.com</a></td>
</tr>
<tr>
<td>51</td>
<td><a href="http://www.thieme-connect.com">www.thieme-connect.com</a></td>
</tr>
<tr>
<td>53</td>
<td>Chia-Po Fu, Elizabeth E. Oczypok, Hira Ali, James P. DeLany, Valerie L. Reeves, Ruey-Feng</td>
</tr>
<tr>
<td>Reference</td>
<td>Title</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>Chang, Erin E. Kershaw.</td>
<td>&quot;Effect of physical activity in a weight loss program on circulating total ANGPTL8 concentrations in northern Americans with obesity: A prospective randomized controlled trial&quot;</td>
</tr>
<tr>
<td>Mohamed Abu-Farha, Jehad Abubaker, Jaakko Tuomilehto.</td>
<td>&quot;ANGPTL8 (betatrophin) role in diabetes and metabolic diseases&quot;</td>
</tr>
<tr>
<td>R W Jeffery.</td>
<td>&quot;Is the obesity epidemic exaggerated? No&quot;</td>
</tr>
</tbody>
</table>
with fibroblast growth factor-21 in women with polycystic ovary syndrome", Journal of Endocrinological Investigation, 2018

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>58</td>
<td>aryamui.ac.ir</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>59</td>
<td>dadun.unav.edu</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>60</td>
<td>erepo.uef.fi</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>61</td>
<td>hdl.handle.net</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>62</td>
<td>journals.physiology.org</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>63</td>
<td>knepublishing.com</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>64</td>
<td>mgmjms.com</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>65</td>
<td>oamjms.eu</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>66</td>
<td>ojs.unpkediri.ac.id</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>67</td>
<td>safpj.co.za</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

Gabriela Paredes-Turrubiarte, Antonio González-Chávez, Ruy Pérez-Tamayo, Beatriz Y. Salazar-Vázquez et al. "Severity of non-alcoholic fatty liver disease is associated with
high systemic levels of tumor necrosis factor alpha and low serum interleukin 10 in morbidly obese patients", Clinical and Experimental Medicine, 2015

Hayes, Nicky. "Doing Psychological Research, 2e", Doing Psychological Research, 2e, 2021


María Rodríguez-Ayllon, Fernando Estévez-López, Cristina Cadenas-Sanchez, Luis Gracia-Marco et al. "Chapter 3 Physical Activity, Sedentary Behaviour and Mental Health in
Nikolaos Perakakis, Georgios A. Triantafyllou, José Manuel Fernández-Real, Joo Young Huh et al. "Physiology and role of irisin in glucose homeostasis", Nature Reviews Endocrinology, 2017
Moderate intensity exercise decreases the circulating level of betatrophin and its correlation among markers of obesity in women