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# Impact of Time-Resricted Feeding and Aerobic Exercise Combination on Promotes Myokine Levels and Improve Body Composition in Obese Women

# Impacto de la combinación de alimentación con restricción de tiempo y ejercicio aeróbico en la promoción de los niveles de mioquinas y la mejora de la composición corporal en mujeres obesas

*Afdhalia Rahma Sari, *Rifat Danendra Risdaryanto, *Mohammad Haidar Pradipta, *Uais Al Qorni, *Purwo Sri Rejeki, *Raden Argarini, **Shariff Halim, *Adi Pranoto
*Universitas Airlangga (Indonesia), **University Technology MARA (UiTM) Pulau Pinang (Malaysia)

**Abstract.** Obesity has been proven to be the cause of various chronic diseases which can increase the risk of premature death. Changing lifestyle through diet and exercise is the best way to overcome the risk of obesity. This study aims to prove the effect of a combination of time-restricted feeding with moderate intensity aerobic exercise on increasing levels of myokines and improving body composition in obese women. A total of 28 obese women aged 20-30 years were involved in the study and were given time-restricted feeding (TRG) and time-restricted feeding and exercise (TREXG) interventions for 2 weeks. ELISA was used to measure PGC-1α and irisin levels in all samples, while TANITA DC-360 was used to measure body composition in the three groups TRG, TREXG, and the control group (CG). The results showed an increase in ΔPGC-1α between CG groups (0.25±2.29 ng/mL) vs TRG (1.64±3.56 ng/mL) vs TREXG (3.68±1.15 ng/mL) and p=0.031. ΔIrisin was also found to increase between CG (405.01±215.71 pg/mL) vs TRG (1443.92±1761.43 pg/mL) vs TREXG (3408.15±1299.85 pg/mL) and p=0.004. TREXG was found to have improved body composition compared to TRG and CG. The main finding of this study was an increase in myokines levels, namely levels of PGC-1α and irisin and there was an improvement in body composition in the time-restricted feeding and exercise group compared to the time restricted-feeding group and the control group in obese women.
**Keywords:** Body composition, exercise, myokine, obesity, time-restricted feeding

**Resumen.** Se ha demostrado que la obesidad es la causa de diversas enfermedades crónicas que pueden aumentar el riesgo de muerte prematura. Cambiar el estilo de vida mediante la dieta y el ejercicio es la mejor manera de superar el riesgo de obesidad. Este estudio tiene como objetivo demostrar el efecto de una combinación de alimentación con restricción de tiempo con ejercicio aeróbico de intensidad moderada sobre el aumento de los niveles de miocinas y la mejora de la composición corporal en mujeres obesas. Un total de 28 mujeres obesas de entre 20 y 30 años participaron en el estudio y recibieron intervenciones de alimentación restringida en el tiempo (TRG) y de alimentación restringida en el tiempo y ejercicio (TREXG) durante 2 semanas. Se utilizó ELISA para medir los niveles de PGC-1α e irisina en todas las muestras, mientras que TANITA DC-360 se utilizó para medir la composición corporal en los tres grupos TRG, TREXG y el grupo de control (CG). Los resultados mostraron un aumento en ΔPGC-1α entre los grupos de GC (0,25±2,29 ng/mL) vs TRG (1,64±3,56 ng/mL) vs TREXG (3,68±1,15 ng/mL) y p=0,031. También se encontró que Δirisina aumenta entre CG (405,01 ± 215,71 pg/ml) frente a TRG (1443,92 ± 1761,43 pg/ml) frente a TREXG (3408,15 ± 1299,85 pg/ml) y p = 0,004. Se descubrió que TREXG mejoró la composición corporal en comparación con TRG y CG. El principal hallazgo de este estudio fue un aumento en los niveles de mioquinas, concretamente los niveles de PGC-1α e irisina, y hubo una mejora en la composición corporal en el grupo de ejercicio y alimentación restringida en el tiempo en comparación con el grupo de alimentación restringida en el tiempo y el grupo de control. en mujeres obesas.
**Palabras clave:** composición corporal, ejercicio, mioquinas, obesidad, alimentación restringida en el tiempo.

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Purwo Sri Rejeki
purwo-s-r@fk.unair.ac.id

## Introduction

The prevalence of obesity in the world by 2025 is estimated to reach 1 billion and around 2.8 million people will die due to obesity (WHO, 2016). The prevalence increased sharply between 1980 and 2019 from 3.2% to 12.2% among men, and from 6% to 15.7% among women (Mathew et al., 2018). This happens in developed and developing countries, such as Indonesia. Currently, obesity sufferers are dominated by women, so efforts to prevent and treat obesity in developing countries will have a significant impact on the world's obese population (Ng et al., 2014). Obesity has been proven to be the cause of various chronic diseases such as type II diabetes mellitus, cancer, obstructive lung disease (Chatterjee et al., 2020) and cardiovascular disease which increases the risk of premature death (Hruby & Hu, 2015). Changing lifestyle through diet and exercise is the best way to overcome the increasing incidence of obesity (Perissiou, 2020). Calorie restriction and exercise have been shown to reduce body weight, improve body composition and reduce risk factors for obesity-related diseases and death (Varady & Hellerstein, 2008; WHO, 2018).

Intermittent fasting (IF) is a form of calorie restriction which has several types, one of which is time-restricted feeding (TRF) (Patterson & Sears, 2017). TRF for 16/8 has been proven to be effective in reducing body weight, improving body composition (Schroder et al., 2021) and reducing the risk of cardiometabolic disease in obese individuals (Cienfuegos et al., 2020). Studies conducted on chronic kidney failure sufferers who are obese have also proven that TRF is beneficial in improving body composition and changing gut microbiota, without causing side effects on kidney function (Lao et al., 2023). This is supported by the fact that TRF is able to increase the metabolic process of nutrients and maintain fitness and muscle function (Kang et al., 2022). It turns out, the positive effects of TRF can be more significant when balanced with exercise. Exercise has the potential to prevent obesity by increasing energy expenditure due to the reduction of adipose tissue and improving body composition (Niemiro et al., 2023). Exercise has the potential to reduce the consequences of obesity, even without weight loss (Petridou et al., 2019). Aerobic exercise has also been shown to reduce waist circumference and visceral adipose tissue (Armstrong et al., 2022). The combination of TRF and exercise was proven to be effective on energy homeostasis resulting in weight loss (Oliveira et al., 2023). Carrying out TRF and exercise simultaneously is an effective diet strategy in reducing fat mass (FM) and increasing fat free mass (FFM) in obese individuals compared to TRF only without a combination of exercise (Kotarsky et al., 2021).

The TRF condition triggers a metabolic switch from glycogenolysis to lipolysis, which generally occurs between 12 and 36 hours during fasting (Anton et al., 2018). PPAR-α will mediate the metabolic switch from glucose to fatty acids through regulating the expression of the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) protein (Anton et al., 2018). PGC-1α is a coactivator that plays a role in fat balance through various metabolic processes (Supruniuk et al., 2017). Individuals who are obese tend to have low levels of PGC-1α (Heinonen et al., 2015; Kobayashi et al., 2021). The condition of obesity causes excessive accumulation of body fat in visceral and subcutaneous white adipose tissue (WAT) (Vidal-Puig, 2013). In contrast, brown adipose tissue (BAT) is believed to be able to fight obesity, with the ability to transfer energy from nutrients to heat (thermogenesis) (Ouellet et al., 2012). When fasting, PGC-1α levels increase significantly because the gluconeogenesis process that occurs increases fat metabolism and suppresses insulin-mediated hepatic glucose production (Besse-Patin et al., 2019).

In line with fasting, exercise can also increase PGC-1α levels significantly (Jung & Kim, 2014; Ruschke et al., 2010). ontraction of large muscle groups during exercise increases the specific expression of PGC1-α and FNDC5 resulting in the release of irisin (Boström et al., 2012). Irisin release modulated by PGC1-α increases UCP-1 (Catalano-Iniesta et al., 2020), and causes fat browning (Perakakis et al., 2017). Irisin is a myokine that plays a role in controlling energy balance, maintaining glucose balance and preventing the occurrence of metabolic syndrome (Perakakis et al., 2017; Merawati et al., 2023). Moderate to high intensity aerobic exercise is able to increase PGC-1α levels both acutely and chronically (Dinas et al., 2017) and stimulates an increase in irisin (Pesce et al., 2020; Rejeki et al., 2021). The combination of IF with exercise has a beneficial effect on fat metabolism (Moraes et al., 2017) especially in controlling body weight (Vieira et al., 2022). The potential of myokines such as PGC-1α and irisin which are induced by fasting and exercise as biomarkers has the potential as a non-pharmacological therapy to reduce the incidence of obesity. However, recent research conducted in humans showed the opposite results that there was no increasing effect of acute or chronic training on PGC-1α and irisin levels in prediabetic subjects (Norheim et al., 2014). Most of the previous research was carried out on experimental animals, while research on human subjects has not been widely studied and the results tend to be paradoxical. Therefore, this study aims to prove the effect of a combination of TRF and moderate intensity aerobic exercise on increasing levels of myokines and improving body composition in obese women.

## Material and Methods

### *Study Design*

This research is a true experimental study with a pretest-posttest group design. Subject recruitment process through social media networks. Inclusion criteria are: Female, age 20 – 30 years, PBF ≥ 40% (very high category), BMI ≥ 25 kg/m2 overweight category, fasting blood glucose ≤ 100 mg/dL, normal hemoglobin (Hb) (12–16 g /dL), normal blood pressure (≥ 110/70 mmHg and ≤ 120/80 mmHg), rest heart rate (RHR) (60-100 bpm) and have a low level of physical activity based on the Global Physical Activity Questionnaire (GPAQ) with a score ≤ 600 METs/minute/week. Meanwhile, the exclusion criteria are: having a history of ulcer disease; diabetes; heart/hypertension; malignancy; alcohol consumption, and smoking during the last 5 years; absence from meetings, aged ≤ 20 years and ≥ 30 years. This research was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Faculty of Medicine, Airlangga University, Surabaya, Indonesia with number (42/EC/KEPK/FKUA/2023).

All subjects underwent health screening before and after intervention with TRF and/with a combination of exercise that lasted for 2 weeks. The post-test was carried out 24 hours after the TRF intervention process and/with the end of the exercise. The number of participants at the start of this study was 58 people, however, with the exclusion criteria causing a large number of sample drop-outs, only 28 people were able to complete all stages of the research until the study ended (Figure 1). Subjects were divided randomly into 3 groups, namely: CG (control group, n = 9), TRG (time-restricted feeding group, n = 10), and TREXG (time-restricted feeding and exercise group, n = 9).

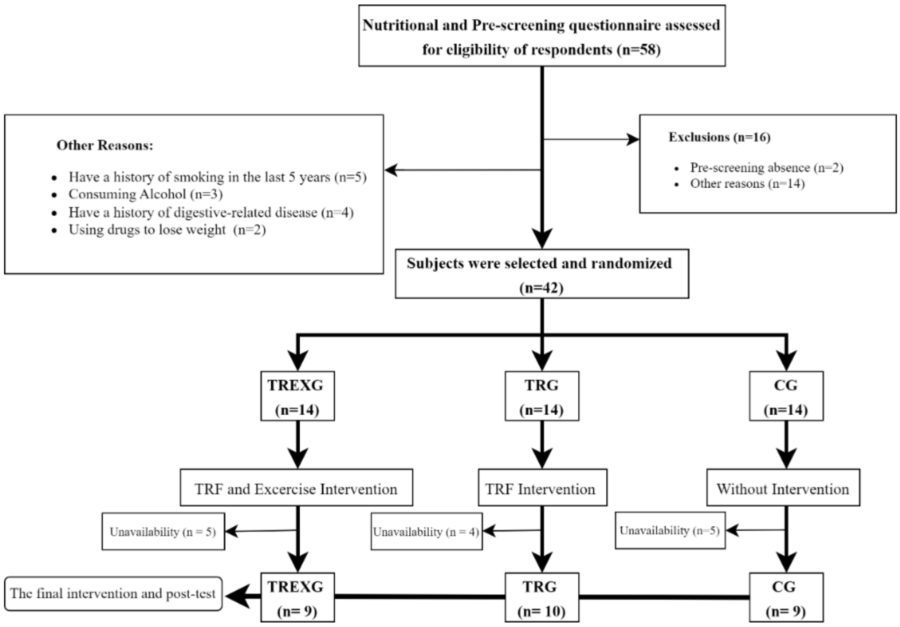


Figure 1. Scheme of procedures for determining research subjects

### *Time Restricted Feeding Protocol*

Intermittent fasting with time-restricted feeding (TRF) 5:2 was applied in this study by fasting 5x/week, on Monday, Tuesday, Wednesday, Thursday and Saturday, for 2 weeks. The TRF protocol that was carried out consisted of 16:8 (8 hours of eating and 16 hours of fasting), while undergoing TRF the subject was allowed to consume water. Subjects were asked to record food during the intervention period using the estimated-food record method. Subjects were given a Food Photo Book or "Buku Foto Makanan" published by the Ministry of Health of the Republic of Indonesia to make it easier for subjects to visually estimate the weight of food consumed. Before the study began, subjects received explanations and training regarding recording food intake and how to use it.

### *Aerobic Exercise Protocol*

In the group that performed a combination of aerobic exercise, exercise was carried out using a treadmill with a moderate intensity of 60-70% HRmax. Exercise is carried out 30 minutes before breaking the fast for 40 minutes (5 minutes warm up (50-60% HRmax), 30 minutes main training (continuous with 60-70% HRmax, and 5 minutes cool down (50-60% HRmax) for 2 weeks with frequency 5x/week, namely on Monday, Tuesday, Wednesday, Thursday and Saturday, for 2 weeks. The active phase of the training session was increased gradually in the form of walking/running on a treadmill. The intensity is increased gradually from 60% to 70% of the maximum HR (HRmax). Calculation of training intensity uses the formula HRmax = 220 – age (Pranoto et al., 2024).

Before training begins, a health profile check is carried out in the form of blood pressure, resting heart rate, oxygen saturation, and body temperature first to determine that the subject is fit to exercise. The intensity of the exercise is controlled using a Polar H10 heart sensor, with room humidity of 50-70% and room temperature of 26 ± 1 °C (Rejeki et al., 2023).

### *Body Composition Assessment*

Body composition was measured during the pre-test and post-test using the TANITA Body Composition Analyzer DC3607601(2)-1604 FA (TANITA Corporation of America, Inc., Arlington Heights, IL, USA) (Pranoto et al., 2023). The data collected was body fat percentage (PBF), fat mass and muscle mass and BMI.

### *Daily Food Intake Assessment*

Subjects in the 3 groups were asked to complete food records for 3 non-consecutive days, namely 2 weekdays and 1 weekend day. The assessment of food intake was analyzed using the Nutri Survey 2007 software (EBISpro, Willstaett, Germany) to calculate the average energy intake and macronutrient intake (carbohydrates, fat and protein) which was then analyzed by comparing it to the recommended Nutritional Adequacy Rates or "Angka Kecukupan Gizi" for Indonesians based on the Republic of Indonesia Minister of Health Regulation No. 28 year 2019. The results of the analysis will be categorized based on criteria in accordance with the recommendations of the 2012 National Food and Nutrition Widyakarya or "Widyakarya Nasional Pangan dan Gizi" (WNPG) which are divided into severe level deficits (≤ 70% of the requirement figure), moderate level deficits (70-90% of the requirement figure), mild level deficit (80-89% of the requirement figure), normal (90-119% of the requirement figure) and above the requirement figure (≥ 120% of the requirement figure) (Kartono et al., 2012).

### *Daily Physical Activity Assessment*

Subjects in the 3 groups were asked to complete daily activity records for 3 non-consecutive days, namely 2 weekdays and 1 weekend day. Daily physical activity assessments were analyzed and converted into METs with reference to Ainsworth, 2011 to calculate the average energy expenditure and daily non-exercise activity categories in the form of daily caloric energy expenditure (Ainsworth et al., 2011).

### *Blood Collection and Serological Analysis*

Blood sample of 4 ml was taken from the cubital vein. The blood taken was then placed in a vacutainer, then centrifuged for 15 minutes at a speed of 3000 rpm. Serum was separated and PGC-1α and irisin levels immediately analyzed at the Physiology Laboratory, Faculty of Medicine, Brawijaya University, Malang. Measurement of PGC-1α levels was carried out using an ELISA kit (Cat. No.: E-EL-H1359; Elabscience, Inc., USA) with a sensitivity level of PGC-1α in the kit of 0.10 ng/mL. Irisin levels were measured using an ELISA kit (Cat.No.: E-EL-H6120; Elabscience, Inc., USA) with a sensitivity level of irisin in the kit of 9.38 pg/mL. The accuracy of the Elisa Kit used has been validated by previous studies (Sugiharto et al., 2021; Esad Tezcan et al., 2022).

### *Statistical Analysis*

The normality test was carried out using the Shapiro-Wilk test, followed by a homogeneity test using the Levene test. Difference tests using paired sample t-test, one-way ANOVA, followed by the Least Significant Difference (LSD) post-hoc test and Pearson product-moment correlation test were used to determine the relationship between PGC-1α and irisin and body composition. All data are presented as mean ± standard deviation (SD). All statistical analyzes used a significance level ($p \leq 0.05$).

## Results

The basic characteristics of several parameters between groups are presented in Table 1. The mean of age, systolic blood pressure (SBP), diastolic blood pressure (DBP), resting heart rate (RHR), oxygen saturation (SpO--2), body temperature (BT), fasting blood glucose (FBG), hemoglobin (Hb), body height (BH), body weight (BW), body mass index (BMI), percent body fat (PBF), fat mass (FM), fat free mass (FFM), skeletal muscle mass (SMM), peroxisome proliferator-activated receptor-γ coactivator 1-α (PGC-1α), and irisin did not have significant differences compared to the control group. The main findings of this study are that there is an increase in PGC-1α and irisin between the pretest and posttest in the time-restricted feeding and exercise group (TREXG) ($p \leq 0.001$), whereas in the time-restricted feeding group (TRG) there was a significant increase in irisin levels ($p \leq 0.05$) and no differences were observed in PGC-1α levels between the pretest and posttest ($p \geq 0.05$) (Figure 2 and 3). PGC-1α and irisin levels did not differ significantly between groups (pretest). However, PGC-1α and irisin levels (posttest and delta) increased significantly after two weeks of intervention compared with the control group. Likewise, body composition was found to improve in TREXG compared to TRG and the control group (CG) (Table 2).

Table 1.
General characteristics of the study subjects

| Variabel | CG; n=9 | TRG; n=10 | TREXG; n=9 | p-Value |
|---|---|---|---|---|
| Age, yrs | 23.67±1.00 | 24.20±2.69 | 22.89±1.83 | 0.376 |
| SBP, mmHg | 114.28±8.51 | 116.65±12.37 | 116.28±10.75 | 0.878 |
| DBP, mmHg | 68.97±4.49 | 73.95±8.55 | 74.17±7.48 | 0.231 |
| RHR, bpm | 80.89±9.57 | 90.50±10.72 | 92.11±16.14 | 0.135 |
| $SpO_2$, % | 98.11±0.78 | 98.80±0.42 | 98.44±0.53 | 0.056 |
| BT, °C | 35.87±0.82 | 35.87±0.58 | 36.23±0.71 | 0.456 |
| FBG, mg/dL | 98.11±27.06 | 97.90±26.24 | 93.00±40.09 | 0.511 |
| Hb, g/dL | 14.40±2.09 | 13.21±1.65 | 14.00±1.73 | 0.365 |
| BH, kg | 1.55±0.04 | 1.57±0.05 | 1.56±0.04 | 0.627 |
| BW, m | 70.43±5.74 | 75.22±13.04 | 78.08±8.95 | 0.270 |
| BMI, $kg/m^2$ | 29.82±2.51 | 31.22±5.01 | 32.23±3.11 | 0.407 |
| PBF, % | 44.38±2.79 | 45.84±4.15 | 48.06±2.89 | 0.085 |
| FM, kg | 31.27±4.39 | 34.93±9.11 | 37.70±6.42 | 0.170 |
| FFM, kg | 38.86±2.34 | 40.29±4.31 | 40.38±2.98 | 0.561 |
| SM, kg | 36.63±2.13 | 37.94±3.93 | 38.00±2.71 | 0.566 |
| PGC-1α, ng/mL | 3.82±2.37 | 3.96±2.34 | 3.57±1.46 | 0.920 |
| Irisin, pg/mL | 5483.12±2300.06 | 5235.97±1670.61 | 5258.69±1748.63 | 0.954 |

Description: CG: Control group; TRG: Time-restricted feeding group; TREXG: Time-restricted feeding and exercise group. Data are presented with mean ± SD. p-Value are obtained by one-way ANOVA test

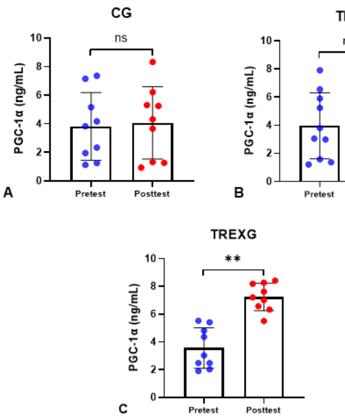


Figure 2. Differences in PGC-1α levels (ng/mL) between pretest and posttest in each group. Description: Data are presented with mean ± SD. p-Value are obtained by paired sample t-test. (ns) No significant to pretest ($p \geq 0.05$). (**) Significant to pretest ($p \leq 0.001$)

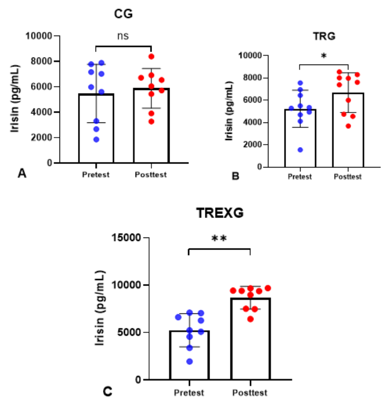


Figure 3. Differences in irisin levels (pg/mL) between pretest and posttest in each group. Description: Data are presented with mean ± SD. p-Value are obtained by paired sample t-test. (ns) No significant to pretest ($p \geq 0.05$). (*) Significant to pretest ($p \leq 0.05$). (**) Significant to pretest ($p \leq 0.001$)

Table 2.
Comparison of myokines levels and body composition variables between CG vs TRG vs TREXG

| Variable | CG; n=9 | TRG; n=10 | TREXG; n=9 | p-Value |
|---|---|---|---|---|
| Pre-PGC-1α, ng/mL | 3.82±2.37 | 3.96±2.34 | 3.57±1.46 | 0.920 |
| Post-PGC-1α, ng/mL | 4.07±2.53 | 5.61±1.72 | 7.24±0.99** | 0.005 |
| Δ-PGC-1α, ng/mL | 0.25±2.29 | 1.64±3.56 | 3.68±1.15** | 0.031 |
| Pre-Irisin, pg/mL | 5483.12±2300.06 | 5235.97±1670.61 | 5258.69±1748.63 | 0.954 |
| Post-Irisin, pg/mL | 5888.13±1558.81 | 6679.89±1781.45 | 8666.85±1201.09**† | 0.002 |
| Δ-Irisin, pg/mL | 405.01±215.71 | 1443.92±1761.43 | 3408.15±1299.85**† | 0.004 |
| Δ-PBF, % | 0.66±0.94 | -0.37±1.02* | -1.06±0.62** | 0.001 |
| Δ-FM, kg | 0.36±0.58 | -0.23±0.75* | -0.64±0.16** | 0.004 |
| Δ-FFM, kg | 0.48±0.39 | -0.37±0.94* | -0.73±0.47** | 0.002 |
| Δ-SM, kg | -0.28±0.63 | 0.02±0.61 | 0.39±0.18* | 0.039 |

Description: (*) Significant at control group (CG) p ≤ 0.05. (**) Significant at control group (CG) p ≤ 0.001. (†) Significant at time-restricted feeding group (TRG) p ≤ 0.05. Data are presented with mean ± SD. p-Value are obtained by one-way ANOVA test and LSD post-hoc test

## Discussion

The aims of this study is to quantify alterations in body composition and myokine level in a sample of 28 obese women, who were categorised into three groups: TREXG, TRG, and CG. The fasting and exercise regimen was implemented at a moderate level of intensity and frequency, occurring five times per week for a duration of two weeks. Participants broke their fast 30 minutes after completing the exercise. Prior to the implementation of the intervention, there were no notable disparities in the distribution of data. As a result, all participants in each intervention group started off in the same initial state and met the predetermined criteria. According to the main results of this study, a) the percentage of body fat (PBF) went down after two weeks of time-restricted feeding (TRF) and moderate intensity aerobic exercise; b) the group that did both TRF and aerobic exercise gained more skeletal muscle mass (SMM) than the group that only did TRF; and c) the group that did both TRF and aerobic exercise had a bigger rise in serum levels of PGC-1α and irisin, as opposed to TRF only.

The prevalence of obesity is generally higher in women than men in various age ranges, primarily because women naturally have a higher proportion of body fat compared to men (Mathew et al., 2018). The participants in this study had a body mass index (BMI) of ≥25 kg/m2, which is considered obese according to the Asia-Pacific population criteria (Pan & Yeh, 2008). Furthermore, the subject also had a very high body fat percentage of ≥40% with an obese nutritional status (Jeukendrup & Gleeson, 2019). The results showed that there was an improvement in body composition (FM, PBF, FFM, dan SMM) and a significant increase in myokine levels (PGC-1α and irisin) in the TREXG and TRG compared to CG. The best improvements in body composition and myokine levels were in the TREXG, followed by TRG, and then CG. Differences in mechanism between fasting and combination with aerobic exercise in the FM, PBF, FFM, and SMM parameters are the background for differences in results of serum PGC-1α and irisin levels.

In this study, there were significant changes in serum PGC-1α and irisin levels between groups that performed TRF and/with a combination of moderate-intensity aerobic exercise. This change can be seen in a greater decrease in percentage of body fat mass in TREXG compared to those who only underwent TRF. The combination of TRF and aerobic exercise is considered effective in increasing fat browning and metabolic switching compared to TRF without exercise. The combination of TRF and exercise is considered better than TRF only in increasing serum PGC-1α and irisin levels. Research conducted on young women with a sedentary lifestyle showed a significant increase in serum irisin levels after carrying out aerobic exercise running on a treadmill for 5x/week for 2 weeks (Torre-Saldaña et al., 2019). Sedentary behavior is a lifestyle that plays a role in the pathophysiology of obesity or overweight (Devi et al., 2023). Meanwhile, research with a longer duration also showed similar results, such as Karras' research in 2021 which also stated that irisin levels increased after fasting 16 hours per day for 7 weeks (Karras et al., 2021) and moderate intensity aerobic exercise by running on a treadmill for 8 weeks with a frequency of 3x/week is effective in increasing plasma irisin levels in obese individuals (Inoue et al., 2020). Research using aerobic exercise 3 times/week with a duration of 50 minutes at an intensity of 70-80% HRmax for 12 weeks was able to increase PGC-1α levels in obese teenagers (Vargas-Ortiz et al., 2015). Based on several studies, it can be seen that TRF intervention and exercise starting 2 weeks can increase serum myokine (PGC-1α and irisin) levels.

Fasting allows a metabolic switch to occur after 10-12 hours, which will produce ketone bodies through the oxidation of fatty acids, which are used as an energy source by the body (de Cabo & Mattson, 2019; Mattson et al., 2014). Time restricted-feeding will stimulate an increase in the expression of PGC-1α which is regulated by AMPK and SIRT1 which causes the induction of fatty acid synthesis, resulting in efficient metabolism in the body (Masaki Kobayashi, Yusuke Deguchi, Yuka Nozaki, & Yoshikazu Higami, 2021). Research on experimental animals (rabbits) with 16 hours of intermittent fasting intervention showed a better increase in PGC-1α levels compared to the control group. In addition, prolonged fasting intervention (> 40 hours) did not show an increase in PGC-1α levels (Antarianto, Kadharusman, Wijaya, & Hardiny, 2023). On the other hand, a group of mice that performed intermittent fasting 2x/week for 8 weeks showed an increase in serum irisin levels, according to research conducted on experimental animals (rats) (Günbatar & Bulduk, 2023). The results of this study indicated no changes in serum PGC-1α levels after 2 weeks of intervention with time-restricted feeding. This is different from research on experimental animals (Antarianto et al., 2023; Günbatar & Bulduk, 2023; She, Sun, Hou, Fang, & Zhang, 2021) which shows that intermittent fasting causes significant changes in levels of PGC-1α and irisin. However, interventions typically last for more than 4 weeks. Until now, research regarding the metabolic switch mechanisms after TRF in humans has been minimal. Time-restricted feeding (TRF) has a significant impact on fat mass and fat-free mass (Chen et al., 2021). Time-restricted feeding triggers the activation of SIRT and AMPK as molecular energy sensors (Rui, 2014). Increased PGC-1α in the liver causes increased fatty acid oxidation and decreased liver triglycerides, which helps reduce VLDL and LDL (Santos & Macedo, 2018). Weight loss occurs due to a decrease in fat mass and fat-free mass, which occurs metabolically (Most & Redman, 2020) and over time results in energy intake and energy expenditure reaching balance and weight loss being achieved (Most & Redman, 2020). This is beneficial for improving body composition in obese individuals (Anton et al., 2018).

Time-restricted feeding (TRF) provides better benefits when combined with exercise. In training adaptation conditions, muscle carbohydrate oxidation capacity increases, thus allowing higher energy expenditure during exercise, as well as increasing fat oxidation and improving exercise performance, which is the main factor in the use of fat as an energy source (Hargreaves & Spriet, 2020). It needs to be understood that more than 30% of the total human body mass consists of skeletal muscle, which plays a role in metabolism and is able to use various substrates such as glycogen, glucose, fatty acids, and creatine phosphate to produce energy (Kumar et al., 2020). Exercise conditions induce more heat production, thereby increasing energy expenditure, which contributes to reduced lipid accumulation in tissues, which has an impact on improving the body composition of obese sufferers (X.-Q. Xiong et al., 2015). This is because fasting and exercise conditions cause skeletal muscle and liver to produce pyruvate through glycogenolysis and glycolysis so that energy expenditure will be much greater (Rui, 2014). Muscle contractions during exercise cause the release of PGC-1α which is regulated by muscle cells during exercise (Remels et al., 2013) which helps increase the effects caused by fasting. Skeletal muscle contraction which will increase PGC-1α expression will interact with the expression of the neuronal gene FNDC5 which plays a role in irisin excretion (Xu, 2013). Irisin levels increase by 35% after 3 minutes of starting physical activity and increase acutely in response to exercise (Daskalopoulou et al., 2014), and have been shown to increase after downhill running training (Tsuchiya, Mizuno, & Goto, 2018) but have not been shown to increase after resistance training (Korkmaz et al., 2019). PGC-1α-modulated irisin from muscle is a myokine that acts specifically on subcutaneous white fat cells and causes them to turn brown by increasing the expression of UCP1 and other thermogenic genes ( Boström et al., 2012 ). Irisin also plays a role in increasing glucose uptake in skeletal muscle via the AMPK pathway (Zhang et al., 2014) and increasing lipolysis via the cAMP pathway (X. Q. Xiong et al., 2015). So time-restricted feeding combined with moderate-intensity exercise was able to increase myokine levels (PGC-1α and irisin) after 2 weeks of intervention even though the duration of the intervention was relatively short. Exercise triggers an energy deficit and increases energy use at the same time, skeletal muscle contraction increases the need for energy metabolism and has an impact on training adaptation which triggers a metabolic shift due to an increase in muscle buffer capacity; while TRF triggers an energy deficit due to calorie restriction carried out. In this study, it is suspected that the metabolism of PGC-1α and irisin in skeletal muscle has a greater role in increasing myokine levels in the combination exercise group compared to the TRF group, which has an impact on improving body composition. This research succeeded in proving that a combination of TRF and/with aerobic exercise for 2 weeks was able to increase serum myokine (PGC-1α and irisin) levels and significantly improve body composition in obese individuals.

The results of the analysis of average daily energy expenditure are in a lower range for daily energy and nutrient intake. Energy and nutrient intake tends to be good because there is no surplus calorie at adlibitum; however, the results of meeting energy adequacy show that all groups have intakes that tend to be below the recommended dietary allowances (RDA) with a moderate deficit category, namely ≤ 2250 kcal/day. This happened unintentionally because the subjects were not asked to eat according to a certain amount of daily intake or follow patterns and guidelines for certain types of diet. This condition turns out to have an effect on creating a negative energy balance, because usually the reduction in intake occurs around 325-480 kcal per day for weight loss (Hill et al., 2012). The results of the analysis of the subjects' average energy and nutrient intake were in the range of 1200-1500 kcal, which is the same as the low-energy diet (Seo et al., 2019) and played a role in helping improve the body composition of obese individuals in this study. The results of the study showed an increase in myokine levels which was followed by improvements in body composition. So the combination of TRF with aerobic exercise can be used as a recommendation in non-pharmacological treatment of obesity.

This research has several limitations, including: a) the time-restricted feeding protocol still needs to be developed properl; even though this study used 5 days/week to carry out TRF, the intake needs were not adjusted to individual needs both in terms of quality and quantity of food consumed. To minimize bias in the study, it is necessary to monitor dietary patterns. b) It is felt that the study duration, which was only 2 weeks, can still be increased to see the impact of long-term fasting and exercise, so a study over a longer period was needed to see the effect of TRF and exercise combination on obesity. c) This study was limited to the female population, so it needs to be carried out on the male population also, considering that obesity can also occur in men. Therefore, a similar study with a personalised nutrition approach with a larger population and using a male population needs to be carried out to get maximum results.

## Conclusion

The main findings of this study were an increase in myokine levels, namely PGC-1α and irisin levels, in the time-restricted feeding and exercise group compared to the time-restricted feeding group and control group. The time-restricted feeding and exercise group was also found to be more effective in improving body composition compared to the other two groups of obese women. Therefore, time-restricted feeding and exercise groups can be recommended as a safe and affordable alternative therapy option to treat obesity problems.

## Conflict of Interest

In this study the authors declare that they have no conflicts of interest.

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| | | |
|---|---|---|
| Afdhalia Rahma Sari | afdhalia.rahma.sari-2022@fk.unair.ac.id | Traductor/a |
| Rifat Danendra Risdayanto | rifat.danen.risdaryanto-2021@fk.unair.ac.id | Traductor/a |
| Mohammad Haidar Pradipta | mohammad.haidar.pradipta-2021@fk.unair.ac.id | Traductor/a |
| Uais Al Qorni | uais.al.qorni-2022@fk.unair.ac.id | Traductor/a |
| Purwo Sri Rejeki | purwo-s-r@fk.unair.ac.id | Traductor/a |
| Raden Argarini | raden-a@fk.unair.ac.id | Traductor/a |
| Shariff Halim | halimshariff@uitm.edu.my | Traductor/a |
| Adi Pranoto | adi.pranoto-2020@fk.unair.ac.id | Traductor/a |