2024, Retos, 55, 289-295


# Physiological Impact Of Aerobic Exercise During Fasting On Inflammatory Risk Factors In Obese Women
# Impacto fisiológico del ejercicio aeróbico durante el ayuno sobre los factores de riesgo inflamatorios en mujeres obesas

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**Abstract.** Physical exercise during fasting is an interesting therapeutic agent in preventing increased inflammation in obesity. Therefore, this study aims to prove the physiological impact of a combination of physical exercise and fasting on inflammatory risk factors in obese women. This research involved 18 obese women as research subjects who met the predetermined criteria and were then randomly selected. Subjects were divided into 2 groups: a control group ($K_1$; n = 9) and a group that combined physical exercise and fasting ($K_2$; n = 9). Physical exercise is done aerobically using a treadmill for 40 minutes at moderate intensity while fasting is done intermittently: fasting for 16 hours, followed by not fasting for 8 hours. The combination of physical exercise and fasting was carried out for 2 weeks. Blood samples were taken to measure the risk of inflammation, using the CRP biomarker, from the cubital vein in as much as 4 mL, which was carried out before and after treatment. Data analysis used a paired sample t-test with a significance level of 5%. Based on the research results, there are significant differences. The level of CRP reduction between the treatment and control groups ($p \leq 0.05$). Based on the results of this research, physiological evidence shows that aerobic exercise during intermittent fasting reduces inflammatory risk factors in obese women. Therefore, aerobic exercise during fasting can be recommended as an approach to reducing inflammatory risk factors in obesity.
**Keywords:** Obese women, aerobic exercise, intermittent fasting, risk of inflammation

**Resumen.** El ejercicio físico durante el ayuno es un agente terapéutico interesante para prevenir el aumento de la inflamación en la obesidad. Por tanto, este estudio tiene como objetivo demostrar el impacto fisiológico de una combinación de ejercicio físico y ayuno sobre los factores de riesgo inflamatorios en mujeres obesas. Esta investigación involucró a 18 mujeres obesas como sujetos de investigación que cumplieron con los criterios predeterminados y luego fueron seleccionadas al azar. Los sujetos se dividieron en 2 grupos: un grupo control ($K_1$; n = 9) y un grupo que combinaba ejercicio físico y ayuno ($K_2$; n = 9). El ejercicio físico se realiza de forma aeróbica utilizando una cinta rodante durante 40 minutos a intensidad moderada mientras que el ayuno se realiza de forma intermitente: ayuno de 16 horas, seguido de no ayuno durante 8 horas. La combinación de ejercicio físico y ayuno se realizó durante 2 semanas. Se tomaron muestras de sangre para medir el riesgo de inflamación, utilizando el biomarcador CRP, de la vena cubital en hasta 4 ml, lo cual se realizó antes y después del tratamiento. El análisis de los datos utilizó una prueba t de muestras pareadas con un nivel de significancia del 5%. Según los resultados de la investigación, existen diferencias significativas. El nivel de reducción de la CRP entre los grupos de tratamiento y control ($p \leq 0.05$). Según los resultados de esta investigación, la evidencia fisiológica muestra que el ejercicio aeróbico durante el ayuno intermitente reduce los factores de riesgo inflamatorios en mujeres obesas. Por lo tanto, se puede recomendar el ejercicio aeróbico durante el ayuno como enfoque para reducir los factores de riesgo inflamatorios en la obesidad.
**Palabras clave:** Mujeres obesas, ejercicio aeróbico, ayuno intermitente, riesgo de inflamación

Fecha recepción: 11-01-24. Fecha de aceptación: 10-03-24
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## Introduction

Obesity is associated with increased risk factors for inflammation, which will increase the health problems that attract the most attention of the world community (Lozano-Vicario & Cedeno-Veloz, 2023). This is related to the complexity that occurs in obesity which will increase metabolic disease (Aryati, 2020). Inflammation in obesity can also have an impact on reducing motivation for physical exercise, not only increasing the accumulation of fat tissue but also being the cause of decreased levels of physical fitness, thus increasing the risk factor for complications (Soehnlein & Libby, 2021). The level of inflammation in obesity has a significant impact on the mobility of obesity which causes white adipose to accumulate ectopically in the visceral cavity, thereby stimulating the formation of plaques containing macrophages and leukocytes throughout the tunica intima layer (Ahmed et al., 2021). This can trigger the release of the synthesis of pro-inflammatory cytokines and proteins (Chupel et al., 2017). Meanwhile, high inflammation causes metabolic disorders such as a collection of risk factors for cardiovascular disease, namely hypertension, hyperglycemia, decreased high-density lipoprotein (HDL), and hypertriglyceridemia (Alizaei Yousefabadi et al., 2021). However, reducing inflammation and improving metabolic health in obesity is still not a major concern. Therefore, interesting and systematic efforts are needed to control inflammatory risk factors.

A non-pharmacological approach that suits the characteristics of obesity is to balance the energy that enters and the energy that leaves the body (Correia et al., 2021). Restricting calories during fasting can reduce adipose tissue but does not have an impact on increasing metabolic performance, heart health, or skeletal muscle performance (Broome et al., 2021). Therefore, doing physical exercise can trigger an increase in metabolic function and other organ systems, which will affect metabolic performance and also the performance ability of skeletal muscles (Ates et al., 2019; Jin et al., 2018). Reducing inflammation can be done by reducing calorie intake, inhibiting calories, and increasing calorie expenditure (Kirk et al., 2020). Several previous studies conducted to improve metabolic function with resistance training during fasting did not find a significant reduction in inflammatory risk factors (Kolahdouzi et al., 2019). Meanwhile, another study by Maaloul et al. (2022) stated that a reduction in inflammatory risk factors was found in the group treated with aerobic exercise during fasting. Therefore, aerobic exercise during fasting will be an effective strategy to reduce and increase the utilization of energy reserves while increasing muscle metabolic capacity (Brocchi et al., 2022).

Aerobic exercise during fasting not only stimulates glycogen utilization but also promotes adaptations to increase the oxidative capacity of skeletal muscle (Kolnes et al., 2021). Changes in oxidative capacity in muscle will increase the ability of mitochondria to transport circulating fatty acids into skeletal muscle and oxidize them to produce ATP while increasing the capacity to catabolize triglycerides during fasting (Kirk et al., 2020). When skeletal muscle contracts and ATP requirements increase, utilization of glucose and lipids (both circulating and intramuscular stores) increases dramatically through the process of lipolysis to break down body fat stores (Bosco et al., 2021). Therefore, regular physical exercise can increase the ability of mitochondrial biogenesis, thus increasing the efficiency of mitochondrial work in breaking down fat (Ye et al., 2019). Increasing metabolism during physical exercise during fasting will not only reduce energy stores but also increase muscle metabolic capacity, thereby reducing adipose tissue and increasing muscle mass, which will reduce the risk of inflammation using the biomarker C-Reactive Protein (CRP). Meanwhile, a combination of aerobic exercise and fasting can be used as a targeted approach to reduce inflammatory risk factors in obesity problems. However, this requires discipline so that there are significant reductions in results.

## Material and Methods

This study was a true experiment with pretest-posttest control group design. The total participants were 18 obese young adult women who met the criteria: age 20–30 years, BMI 25–35 kg/m², body fat percentage ≥ 30%, normal blood pressure, normal resting heart rate, normal hemoglobin, normal oxygen saturation, normal blood sugar, not smoking, not drinking alcohol, and not on a diet. The subject sampling technique uses Consecutive Sampling and division into groups uses random sampling. Then the subjects were divided into two groups: the control group ($K_1$; n=9) and the fasted aerobic exercise group ($K_2$; n=9). All subjects had received information about the intervention in the study verbally and in writing before participating in this study. Subjects voluntarily expressed their agreement to participate by filling out and signing informed consent consciously. The intervention was implemented and supervised by personal trainers from Atlas Sports Club Malang (Indonesia). Moderate-intensity aerobic exercise (60–70% $HR_{max}$) was done by running on a treadmill for 40 minutes while fasting was done for 16 hours (18.00 to 10.00) intermittently, with a frequency of 5x/week for 2 weeks. During exercise, heart rate was monitored using Polar Heart Rate H10 (Pranoto et al., 2024). The environment used for the intervention location has a room temperature of 26±1 °C with a room humidity level of 50-70% (Rejeki et al., 2023). CRP measurements as a biomarker of inflammatory risk factors were carried out before treatment and after treatment. Meanwhile, blood samples were taken one week before treatment and 24 hours after treatment. All procedures in this research comply with the provisions of ethical commission No.42/EC/KEPK/FKUA/2023. Inflammation measurement with the CRP biomarker uses the ELISA Kits method (Cat.No.: E-EL-H0043; Elabscience, Inc., USA) with a CRP sensitivity level in the kit of 0.23 ng/mL and a CRP standard curve range of 0.39-25 ng/mL. Data analysis used the Statistical Package For The Social Science (SPSS) application version 21.0. Data that was normally distributed will be tested for homogeneity using Levene's test. Data that was normally distributed and has a homogeneous variance will be subjected to a paired sample test and independent sample t-test, and followed by effect size evaluation using Cohen's d. The correlation test was applied with Pearson's product moment correlation coefficient (PPMCC). Data are presented as mean ± standard deviation (SD). All statistical analyzes use a significance level of 5%.

## Results

This study aims to reveal the physiological impact of fasting aerobic exercise on inflammatory risk factors. Based on the research results, it shows that there are no significant differences in the average characteristics of research subjects between groups, so that both groups are at the same basic point (Table 1). Meanwhile, the main finding of this study was that there was a difference in the reduction of inflammation between the control group and the treatment group, this was shown by a decrease in the average CRP levels between the pretest and posttest in both groups (Figure 1).

Table 1.
Characteristics of research subjects between groups

| Variable | Group | | p-value |
|---|---|---|---|
| | Control ($K_1$; n=9) | Combination ($K_2$; n=9) | |
| Age (yrs) | 22.6±1.73 | 23.37±2.38 | 0.501 |
| SBP (mmHg) | 112.72±6.47 | 115.06±3.46 | 0.363 |
| DBP (mmHg) | 69.36±5.50 | 71.93±8.55 | 0.481 |
| RHR (bpm) | 76.66±8.33 | 74.75±3.41 | 0.540 |
| $SpO_2$ (%) | 97.55±1.13 | 97.62±1.68 | 0.923 |
| Weight (kg) | 71.60±4.44 | 73.68±8.65 | 0.553 |
| Height (m) | 1.55±0.03 | 1.57±0.05 | 0.270 |
| BMI (kg/m²) | 29.92±1.97 | 29.57±1.93 | 0.719 |

Description: SBP: systolic blood pressure; DBP: diastolic blood pressure; RHR: resting heart rate; $SpO_2$: oxygen saturation; BMI: body mass index. Data are presented as mean ± SD.

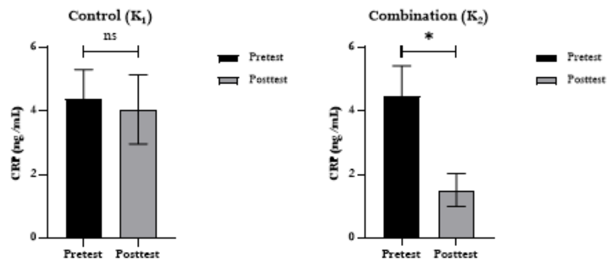


Figure 1. Results of analysis of pretest and posttest CRP levels in each group. Description: $K_1$: Control Group; $K_2$: Combination Group. (ns) Not significant. (*) Indicates a significant value with a pretest ($p \leq 0.05$).

The results of the analysis of the physiological impact of aerobic exercise with fasting on inflammatory risk factors showed a decrease in inflammatory risk factors between the control group and the treatment group. The control group did not show a significant reduction in inflammatory risk factors between before and after treatment. The results of the different test analyses showed that there was a difference in the level of reduction in inflammation as indicated by a decrease in CRP between the control group and the treatment group ($p=0.649$; $p \geq 0.05$). In contrast, the treatment group showed a significant decrease in inflammatory factors between before and after treatment. CRP levels before treatment were 4.47 ng/mL and decreased after treatment to 1.51 ng/mL. In the CRP treatment group, it decreased by 2.96 ng/mL ($p=0.007$; $p \leq 0.05$) and has a large effect size with a Cohen's d value of 3.903.

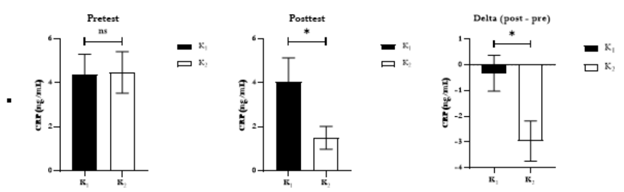


Figure 2. Results of analysis of CRP levels between $K_1$ vs $K_2$ (pre, post, delta). Description: $K_1$: Control Group; $K_2$: Combination Group. (ns) Not significant. (*) Indicates a significant value with a $K_1$ ($p \leq 0.05$).

CRP levels in the posttest in the combination group ($K_2$) were found to be lower than the CRP levels in the control group ($K_1$) (4.05±1.09 vs 1.51± 0.52 ng/mL; $p=0.001$) and has a large effect size with a Cohen's d value of 2.983. Likewise, delta CRP levels in the combination group ($K_2$) were also found to be lower than CRP levels in the control group ($K_1$) (4.05 ± 1.09 vs 1.51 ± 0.52 ng/mL; $p = 0.001$) and has a large effect size with a Cohen's d value of 3.555.

## Discussion

Based on the research results, there was a difference in reducing inflammation before treatment and after treatment, as well as a difference in reducing inflammation between the control group and the treatment group. This was shown by the decrease in CRP between the control group and the training group with a combination of fasting. Previous research results stated that exercise during fasting had a significant impact on reducing inflammatory risk factors. Research conducted by (Augusto et al., 2023) reported that there was a significant reduction in inflammation as indicated by a decrease in CRP levels in the combination group with aerobic exercise when fasting for 16 hours compared to the control group and the fasting group without exercise. Another study by Allen et al., (2020) also stated that there was a significant reduction in inflammation as indicated by the CRP biomarker in the group treated with aerobic exercise with 16 hours of fasting compared to the control group. Then, Kolahdouzi et al., (2019) stated that there was a decrease in inflammation, which was characterized by a decrease in CRP from 4.2mg/L to 2.9mg/L after doing aerobic exercise while fasting for 16 hours for 2 weeks.

The reduction in inflammatory risk factors in the fasting exercise group is thought to be influenced by a decrease in the percentage of fat mass, which is supported by an increase in muscle mass (Nuraini & Murbawani, 2019; Pranoto et al., 2023b). Calorie restriction and weight reduction reduce inflammation, which is characterized by a decrease in the concentration of CRP and most cytokines produced by macrophages in adipose tissue after a periodic fat breakdown process (Zouhal et al., 2020). A fat breakdown will be significant if accompanied by aerobic exercise during fasting because it can increase the regulation of the energy system, which will activate MAPK signaling to stimulate an increase in neutrophils producing antioxidants and anti-inflammatory cytokines to suppress CRP synthesis in the liver by IL-6 and IL-1β (Faris et al., 2019). Therefore, there will be a balance between incoming energy intake and energy expended related to a reduction in inflammatory risk factors due to an increase in the body's metabolic homeostasis (Gonzalo-Encabo et al., 2021).

Fasting reduces energy intake through the management of the fasting energy system (Correia et al., 2021). Fasting utilizes calorie restriction by controlling blood sugar levels as a source of basal energy (Cordon et al., 2021). Then, 3–4 hours after the last food is absorbed by the body, the body will enter the post-absorption phase (Gonzalez et al., 2020). In this phase, blood sugar levels in the body will be reused as energy through the glycolysis process (Elsworth et al., 2023). When the demand for sugar in the body increases, the liver and muscles release glycogen to produce glucose through gluconeogenesis and glycogenesis (Kirk et al., 2020). Blood sugar levels will continue to decrease so that insulin works to maintain glucose homeostasis by suppressing gluconeogenesis and glycogenesis processes to increase glucose uptake by peripheral tissues, especially adipose tissue and skeletal muscle, with the help of glucose transporters (GLUT) (Flores-Opazo et al., 2019). In this case, facilitative transport occurs, which causes glucose to diffuse passively into muscle and adipose tissue without requiring ATP, namely using GLUT-4, which is in muscle and adipose tissue (Knudsen et al., 2020). GLUT4 expression and mitochondrial biogenesis can be gradually increased to supply energy to maintain homeostasis in response to exercise during fasting (Park et al., 2020). GLUT-4 increases the expression of the proliferator-activated-receptor gamma coactivator-1α (PGC-1α) gene as the main regulator of mitochondrial biogenesis, which plays its role in thermogenesis, oxidative phosphorylation, fatty acid metabolism, and regulation of antioxidant transcription factors, resulting in a significant decrease in adiposity, which is followed by decreasing CRP levels as a risk factor for inflammation through modulating the Mitogen-activated Protein Kinase (MAPK) pathway (Abu Shelbayeh et al., 2023).

Aerobic exercise requires oxygen to provide energy in response to muscle contractions (Holsbrekken et al., 2023). The ever-increasing need for oxygen during aerobic exercise causes mitochondria to produce reactive oxygen species (ROS) (Rius-Pérez et al., 2020). High levels of ROS in mitochondria trigger an increase in the transcription factor PGC-1α (via the P38/MAPK signaling pathway) as a key regulator of mitochondrial biogenesis in skeletal muscle (Snezhkina et al., 2020). PGC-1α regulates homeostasis by blocking the activity of Nuclear Factor-Kappa Betta (NFkβ) against genes encoding pro-inflammatory cytokines and oxidative stress produced during exercise (Abu Shelbayeh et al., 2023). So, to rebalance the body's homeostasis, it is necessary to increase the endogenous antioxidant enzymatic cascade through Nrf2 regulation (Thiruvengadam et al., 2021). Then Nrf2 will translocate into the nucleus to join and bind the Antioxidant Response Element (ARE) to become nrf2-ARE to activate antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx) as a form of self-defense (Soman et al., 2023). Nrf2-ARE stimulates neutrophils through glutathione activation to induce the secretion of IL-8 (controls inflammation and healing) and IL-10 (activates anti-inflammatory and strong immunity in myokine cell function against acute and chronic inflammation) to inhibit macrophages in the secretion of IL-1, IL-6, and CRP resulting in a reduction in inflammatory risk factors (Alizaei Yousefabadi et al., 2021; Jin et al., 2018).

Aerobic exercise during fasting can also increase the dismantling of fat energy stores mediated by the MAPK-PGC-1α pathway through thermogenesis, thereby triggering a decrease in CRP levels as a risk factor for inflammation (Ye et al., 2019). During exercise, muscles will activate the Guanine-Nucleotide Exchange Factor (GEF) to stimulate the release of Guanosine Diphosphate (GDP) to allow the binding of Guanosine Triphosphate (GTP) (Soleimani et al., 2019). Then GTPase will activate the MAPK pathway to increase PGC-1α gene expression more (Jin et al., 2018). Activation of PGC-1α stimulates the secretion of FNDC-5 containing fibronectin type III domains, which induces the release of irisin into the blood circulation (Lozano-Vicario & Cedeno-Veloz, 2023; Sari et al., 2024). The release of irisin will trigger the browning process (thermogenesis) in white adipose tissue by stimulating the expression of the Uncoupling Protein-1 (UCP-1) gene, as well as increasing energy expenditure and reducing the accumulation of fat-containing macrophages and pro-inflammatory cytokines, so that a decrease in adipose tissue can affect the rate of decrease in CRP, IL-6, and TNF-α levels (Fatouros, 2018).

The reduced risk of inflammation in the combination of exercise and fasting may also be due to increased energy expenditure during exercise and calorie restriction during fasting. This causes fat accumulation in the body to decrease, where macrophages in adipose tissue decrease along with increased muscle tissue regeneration to suppress IL-6 secretion by macrophages, resulting in a decrease in CRP levels synthesized by the liver (Kolnes et al., 2021). These results follow research conducted by Malinowski et al., (2019) who reported that the beneficial effects of a combination of fasting and aerobic exercise were to reduce body weight, reduce body fat percentage, and limit the risk of developing cardiovascular disease by reducing the synthesis of pro-inflammatory cytokines (such as IL-6 and TNF-α to suppress CRP synthesis) and increasing blood flow. Research by Kotarsky et al., (2021) also reported that aerobic exercise while fasting has been proven to stimulate fat dismantling when glycogen reserves are depleted, thus having an impact on reducing inflammatory risk factors as indicated by a decrease in CRP. Bosco et al., (2021) reported that mobilization and the use of fatty acids in adipocytes increase calorie expenditure, which can prevent the risk of inflammation in obesity, and Real-Hohn et al., (2018) stated that weight loss after exercising while fasting positively influences the state of inflammation through reducing adipose tissue and expression. CRP gene in adipocytes and macrophages significantly.

Aerobic exercise while fasting increases fat oxidation and produces improvements in body composition, fat metabolism, inflammation, and liver function (Banjac et al., 2021). This shows that exercising while fasting can be an effective strategy to help obese sufferers lose weight and improve their quality of health (Soman et al., 2023). Therefore, the aerobic exercise program during fasting is expected to create a balance between energy intake and energy expended through physical activity. If adipose decreases, IL-6 induced in adipose cell macrophages will decrease along with CRP, and anti-inflammatory sensitivity will increase along with increasing muscle tissue mass (Abshirini et al., 2020). The results of this study can contribute to reducing the risk of inflammation-related diseases in obesity. However, this study also has limitations, such as not being able to control the food intake consumed every day and the subject's physical activity outside the study period, so that future research can control these two factors. In addition, observation inflammatory biomarkers only uses one parameter, namely CRP levels so that future research can add other inflammatory biomarkers including Interferon-γ (IFN-γ), interleukins 1β, 6, 8, and Tumor necrosis factor alpha (TNF-α). These variables contribute to limiting the risk of cardiovascular disease in obese.

## Conclusion

Based on the research results, it was concluded that an aerobic exercise program with a moderate intensity of 60–70% HRmax during fasting (16 hours of fasting and 8 hours of eating) and a frequency of 5x/week carried out for 2 weeks affected reducing inflammation levels, as indicated by a decrease in CRP in obese women. Therefore, an aerobic exercise program while fasting for 2 weeks has a good impact on the body's metabolism and reduces inflammatory risk factors.

## Conflict of interest

The authors declare no conflict of interest.

## Funding

This study was supported by research funds Riset Kolaborasi Indonesia (RKI) Universitas Negeri Malang with grant number: 10.5.58/UN32.20.1/LT/2023.

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