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ORIGINAL ARTICLE

Effectiveness of Exercise and Sex Interaction on Adipokines in Obese Rats

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Abstract

Background/Aim: Obesity is a low-grade chronic inflammatory state that promotes a pro-inflammatory immune response. Exercise is considered to be able to prevent inflammation in obesity. The main objective was to determine the effect of the interaction between exercise and sex on inflammation and adipokine in obese rats.

Methods: This research is an experiment using a factorial design with a post-test only. The subjects of this study were 30 Sprague Dawley rats. The rats were 4 months old and weighed 120 g. The rats were given a diet high in carbohydrates and fats. Lee's obesity index was used to measure rats' obesity. The obese rats were then randomly divided into six groups to be given exercise interventions. The intervention provided consisted of aerobic exercise and anaerobic exercise. The primary outcome is adiponectin, leptin, dipeptidyl peptidase-4 (DPP4), tumour necrosis factor alpha (TNF-α) and adipose tissue hypertrophy.

Results: The study found that increased serum adiponectin levels were influenced by exercise ($p < 0.05$) and the interaction between exercise and gender ($p < 0.05$). Decreased serum leptin levels were influenced by gender ($p < 0.05$) and exercise ($p < 0.05$). Decreased serum DPP4 levels were influenced by exercise ($p < 0.05$). Decreased TNF-α expression was influenced by gender ($p < 0.05$) and the interaction between gender and exercise ($p < 0.05$). Decreased adipose cell size was influenced by gender ($p < 0.05$).

Conclusion: This study found that aerobic exercise, anaerobic exercise and the interaction between sex and exercise significantly increased serum adiponectin and decreased TNF-α expression.

Key words: Obesity; Inflammation; Exercise; Adipokines; Sex.

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Introduction

Energy imbalance between food intake and energy expenditure will lead to obesity. Low-grade chronic inflammation is associated with obesity, providing signals promoting pro-inflammatory and persistent immunity.[1, 2] Adipose tissue plays an essential role in regulating obesity.[3] In obesity, the size of adipocytes increases (hypertrophy), consequently increasing macrophage infiltration and ultimately increasing the secretion of various inflammatory cytokines, such as tumour necrosis factor alpha (TNF-α).[4] TNF-α is a cytokine that regulates glucose and lipid metabolism and increases its concentration in obese patients.[5]

White adipose tissue (WAT) is the primary place for storing excess energy in animals with triacylglycerol stored in adipocytes. WAT targets various hormones and adipokines produced by active endocrine organs, namely polypeptides that act on multiple organs and tissues (muscle, liver and hypothalamus) for general physiological and metabolic regulation. In obesity, several adipokines, such as adiponectin levels, decrease while leptin production increases.[6] White adipose tissue produces and secretes leptin, whereas peripheral metabolic tissues and the brain secrete leptin receptors. Leptin is essential in appetite suppression and increased energy expenditure, a core component in obesity prevention.[7] Dipeptidyl peptidase 4 (DPP4) can affect adipogenesis, adipocyte inflammation and insulin sensitivity.[8] The plasma activity of DPP4 increases with obesity. The study's results explain that adipose tissue releases proinflammatory adipokines, including circulating soluble DPP-4 (sDPP4).[9]

Chronic low-grade inflammation can be reduced by reducing body fat, which increases the production of anti-inflammatory cytokines such as adiponectin. Aerobic exercise is an intervention that can reduce body fat and has anti-inflammatory properties,[10] protects against diseases associated with chronic low-grade inflammation in obesity[11] and aerobic exercise can lower adipocyte size and lipid content, resulting in a decrease in adiposity.[12] Anaerobic exercise causes the body to burn more calories and improve insulin sensitivity for hours after rest. It can effectively reduce fat and insulin sensitivity in the body, affect cytokine regulation and maintain a balanced antioxidant status.[13] Aerobic and anaerobic exercise has extraordinarily beneficial non-pharmacological effects on various functional systems of the human body.[14] Although the beneficial mechanisms of aerobic and anaerobic exercise are unknown, several biological mechanisms have been studied, namely decreased visceral adiposity, triglycerides and low-density lipoproteins,[15] increased high-density lipoproteins,[16, 17] decreased blood pressure,[18] decreased systemic inflammation[19] and increased insulin sensitivity.[20]

Based on the background explanation above, researchers are interested in researching the interaction effects of physical exercise and sex on obese rats. This study hypothesises that there is an effect of exercise (aerobic and anaerobic) interaction with sex on the decrease in TNF-α, increase in adiponectin, decrease in leptin, DPP4 and hypertrophy of adipose tissue in obese model rats. The study aimed to determine what effects aerobic exercise, anaerobic exercise and sex could have on adipokines in obese rats.

Methods

Design

This research was an experiment using a factorial design 2x2 with a post-test only.[21, 22] This research was conducted at the Integrated Biomedical Laboratory of the Faculty of Medicine, Udayana University. Male and female Sprague-Dawley rats aged 4 months and weighing 120 g were included in this study. Rats were placed in a temperature-controlled room (20-22 °C). The method of calculating the sample size was based on the ANOVA calculation and had an "E" value called the degree of freedom, between 10 and 20. If the value of E was less than 10, then the number of animals was increased and if the value of E was more than 20, then there were enough animals for the experiment. Any sample size with an E value between 10 and 20 was sufficient. The following equation can calculate the value of E: E = Number of animals + Number of groups.[23] Based on these calculations, the animal sample size in this study was 5.

Obese rats that met the obesity Lee index[24, 25] were randomly divided into three groups: obese rats given aerobic physical exercise, anaerobic physical exercise and obese rats without physical exercise as a baseline. After further intervention, the rats were sacrificed for adipose tissue and blood.

Preparation of rat obesity model

The experimental animals used in this study were 30 Sprague-Dawley rats (*Rattus norvegicus*) obtained from the Faculty of Medicine, Udayana University. Adult male rats were 4-5 months old. Standard rat feed comprises 26 % protein, 63 % carbohydrates and 11 % fat, but in high-fat feed, the composition changes, with 58 % of energy coming from fat.[26] Rats were given a diet high in carbohydrates and fats consisting of 22 % carbohydrates, 58 % fat and 10 % protein obtained from Udayana University. The diet was given *ad libitum*, 1x / day, 30 g/rat, for 4

weeks before treatment and continued until treatment was completed. Obesity criteria in rats was obtained by calculating Lee obesity index = $\sqrt[3]{}$ body weight (g) x 10 / Nasoanal length (mm). Rats were declared obese if the Lee obesity index value was > 0.300.[24, 25]

Exercise

The research equipment used to maintain experimental animals was a plastic tub measuring 45 x 35.5 x 14.5 cm^3, a cage lid made of woven wire measuring 36.5 x 28 x 15.5 cm^3, water bottles and trash. Rats swimming exercises were performed using a divided box of acrylic measuring 37 x 30 x 50 cm^3 with a water depth of 50 cm. Before swimming training began, rats were adapted for 3-5 minutes to adjust to a water temperature of 33 ± 1 °C. Anaerobic exercise were performed on days 1 and 2, 3 and 4 and 5 and 6, rats swam with loads of 10 %, 13 % and 15 % of body mass. The exercise lasted 8 x 10 seconds for 6 days, with an interval of 40 seconds between swimming.[27] In aerobic exercise, the rats swam initially for 10 minutes, then increased their swim time by 10 minutes each week to 60 minutes. Next, exercise time was maintained at 60 minutes until day 30/4 of the week.[28, 29]

Adipokines profile

Forty-eight hours after the last training session, 0.5 mL of venous blood was collected via a retro-orbital vein in all the rats. In these samples, adiponectin, leptin and DPP4 were measured by using an ELISA kit. Adiponectin ELISA Kit, Cat. No E0758Ra. Leptin ELISA Kit, Cat. No E0561Ra. Dipeptidyl Peptidase 4 ELISA Kit, Cat. No E0226Ra (*Bioassay Technology Laboratory*, Shanghai, China).

Tissue preparation and histological examination
After the exercise intervention, the rats were sacrificed using a ketamine xylazine dose of 0.1 mg/200 g body weight. White adipose tissue was isolated from subcutaneous fat, fixed in formalin and embedded in paraffin. Five-micrometre slices were cut using a Leica RM550 rotary microtome (*Leica*, Vienna, Austria). The slices were sketched with Mayer Himalayan and eosin. The slides were examined using an Olympus CX41 microscope and an *OptilabPro* camera using *OptilabPro* software.

Immunohistochemistry

Immunohistochemistry for TNF-a was performed on white adipose tissue using a Kit (Dako EnVision®+ Dual Link System-HRP (DAB+)). Unstained five-micrometre sections were deparaffinised with xylene and rehydrated in a graded ethanol series. Endogenous peroxidase activity was inhibited by 0.3 % H_2O_2. Slides were microwaved using a heat-induced epitope retrieval technique for 3 minutes in tri-sodium citrate buffer. Slides were incubated overnight with anti-TNF-a polyclonal antibody at a dilution of 1:250.

Data analysis

The Kolmogorov-Smirnov test verified the data's normality for all variables. Two-way variance analysis determined the main effects of the type of physical exercise (aerobic and anaerobic exercise), sex and their interaction on serum and adipose tissue variables. A statistically significant difference was considered to be at the level of 0.05. SPSS software, version 16.0, was used for data analysis.

Results

Table 1 shows the results of weight changes and the Lee index. Obese rats that followed aerobic and anaerobic exercise did not change their weight and the Lee index compared to obese rats that did not follow the exercise. Sex affected weight change ($p = 0.000$) and the Lee index ($p = 0.000$) of obese rats who participated in aerobic and anaerobic exercise and did not exercise. Changes in Lee's index were found to be influenced by gender and exercise interaction ($p = 0.038$).

The results of the study (Table 2) found that aerobic exercise and anaerobic exercise were able to increase serum adiponectin levels, serum leptin levels, TNF-α expression (Figure 1) and decrease in adipose cell size (Figure 2) compared to obese rats who did not exercise. The difference in serum adiponectin levels was influenced by exercise ($p = 0.000$) and the interaction between exercise and sex ($p = 0.002$). The difference in serum leptin levels was influenced by sex ($p = 0.032$) and exercise ($p = 0.000$). The difference in serum levels of DPP4 was influenced by exercise ($p = 0.026$). The difference in TNF-α expression was influenced by sex ($p = 0.000$) and the interaction between sex and exercise ($p = 0.012$). The decrease in adipose cell size was affected by sex ($p = 0.000$).

Table 1: Changes in the body weight and Lee index after exercise (n = 30)

Variables	Group (Mean ± SD)			Two-Way ANOVA p-value		
	Aerobic exercise	Anaerobic exercise	Obese	Sex	Exercise	Interaction Sex*Exercise
Initial body weight	222.80 ± 52.57	222.30 ± 60.83	206.80 ± 40.51	-	-	-
Final body weight	221.10 ± 39.82	217.70 ± 53.10	212.90 ± 40.19	0.000	0.695	0.170
Initial Lee index	3.62 ± 0.58	3.60 ± 0.56	3.43 ± 0.39	-	-	-
Final Lee index	3.37 ± 0.40	3.15 ± 0.68	3.49 ± 0.50	0.000	0.423	0.038

Table 2: Mean comparison of adipokines after exercise (n = 30)

Variables	Group (Mean ± SD)			Two-Way ANOVA p-value		
	Aerobic exercise	Anaerobic exercise	Obese	Sex	Exercise	Interaction Sex*Exercise
Adiponectin (mg/L)	3.72 ± 0.29*	4.01 ± 0.47*	2.61 ± 0.97	0.356	0.000	0.002
Leptin (ng/mL)	1.67 ± 0.21*	2.07 ± 0.46*	2.58 ± 0.42	0.032	0.000	0.112
DPP4 (mg/L)	94.39 ± 13.04	91.17 ± 16.26*	111.29 ± 20.22	0.113	0.026	0.626
TNF-α	21.70 ± 10.72	26.20 ± 6.71	26.80 ± 6.95	0.000	0.091	0.012
Adipose tissue hypertrophy (μm)	261.72 ± 102.19	266.81 ± 93.49	315.47 ± 106.49	0.000	0.086	0.680

** Statistically significant at p < 0.05, Two-Way ANOVA post hoc test; DDP4: dipeptidyl peptidase 4; TNF-α: tumour necrosis factor alpha;*

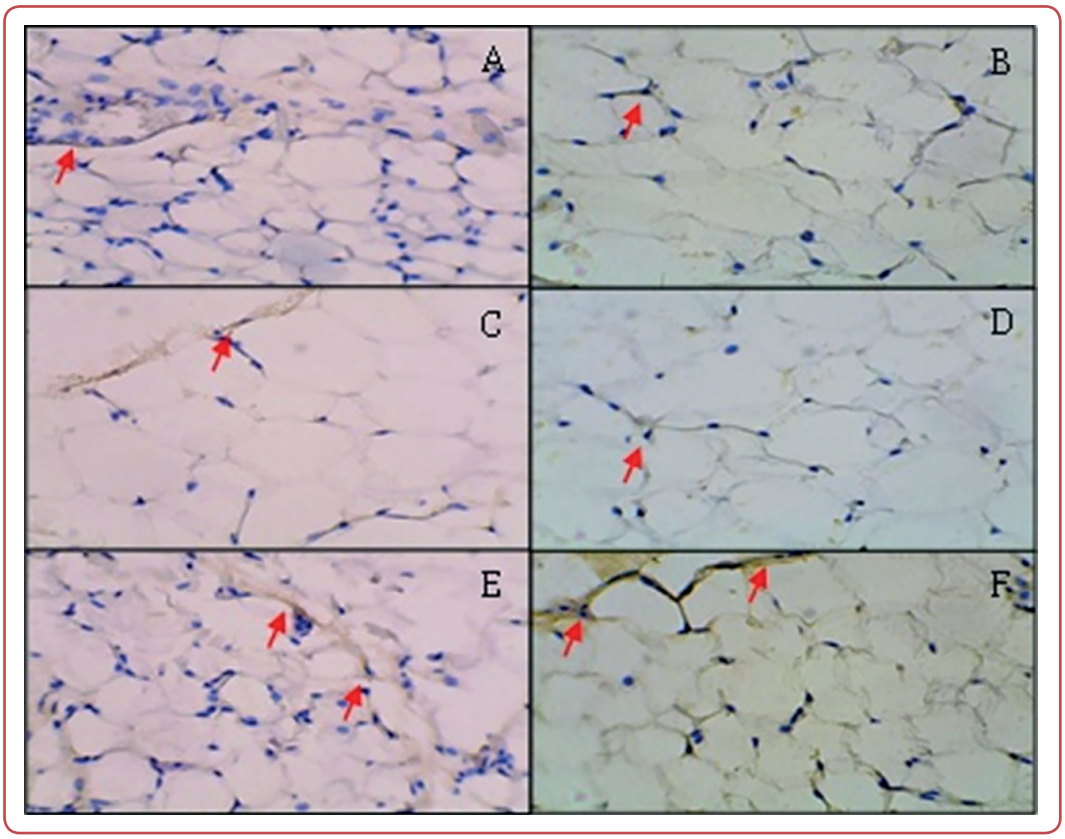

Figure 1: Immunohistochemistry (IHC) staining of tumour necrosis factor alpha (TNF-α) adipose tissue. IHC staining was performed on adipose tissue from aerobic exercise group, anaerobic exercise group and obesity group n = 10/group. A: IHC staining of TNF-α adipose tissue of aerobic exercise male rats; B: aerobic exercise female rats; C: anaerobic exercise male rats; D: anaerobic exercise female rats; E: obese male rats; F: obese female rats.

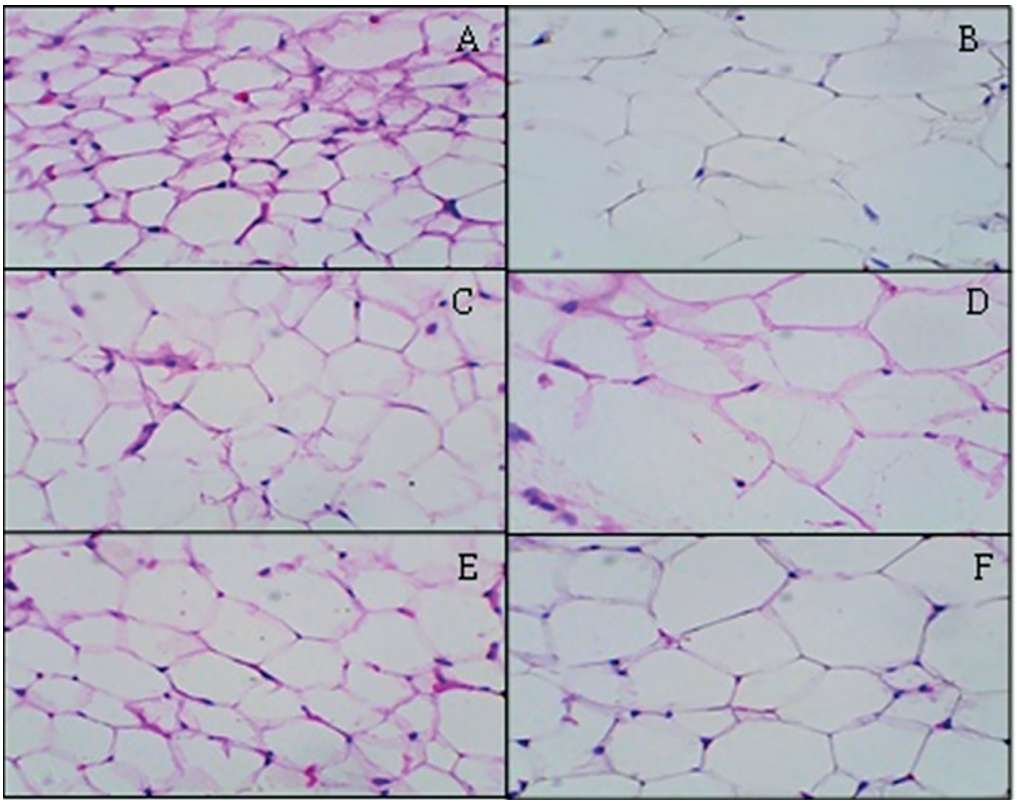

Figure 2: Haematoxylin and eosin staining of adipose tissue. Representative images of haematoxylin and eosin staining performed on adipose tissue from aerobic exercise group (AE), anaerobic exercise group (AnE) and obese group (OB) n = 10/group. A: the adipose tissue cell size of aerobic exercise male rats; B: aerobic exercise female rats; C: anaerobic exercise male rats; D: anaerobic exercise female rats; E: obese male rats; F: obese female rats.

Discussion

This study found that sex affects the final body weight and final index of obese rats. The interaction of exercise and gender affects the decrease in the level of obesity in rats. Aerobic exercise and anaerobic exercise increase serum adiponectin and decrease serum leptin. A decrease in serum DPP4 was found in obese rats that had done anaerobic exercise. A decrease in serum leptin, a reduction in TNF-α expression and a decrease in adipose tissue were influenced by sex. The study also found an interaction effect between sex and exercise on decreasing serum adiponectin and decreasing TNF-α expression.

Aerobic exercise can reduce TNF-α in obese male rats, while anaerobic exercise can reduce TNF-α. Research by Jiménez-Maldonado et al found the same thing when running exercise in male mice reduced TNF-α.[30] Santiago et al found that resistance training for 8 weeks can reduce TNF-α in 27 women.[31] A study conducted by Rejeki et al found that aerobic exercise can reduce leptin levels.[32] The study found that exercise in obesity decreases leptin and increases leptin resistance.[33] Bharath et al found decreased body weight, decreased waist circumference and low plasma leptin levels in obese individuals who underwent anaerobic and aerobic exercise.[34] However, each gender effect study used the same training session.

This study found an interaction between exercise type and gender on adiponectin levels. Sex is important to an inflammatory response. A comparison of eutrophic groups showed that women had a lower inflammatory status than men. Obese men and women both showed a significantly increased inflammatory response

compared to the eutrophic group, with explicit sex dimorphism in inflammatory profiles in adolescent obesity.[35] Aerobic exercise performed by obese male rats can increase adiponectin levels, while obese rats that perform anaerobic exercise increase adiponectin levels. Garekani et al found that aerobic running exercise in obese rats can increase adiponectin levels.[36] Rejeki et al also studied the effects of anaerobic exercise in obese women and found that it can increase adiponectin levels.[32] Exercise is a safe and inexpensive non-pharmacological intervention to interfere with metabolism.[37, 38] Researchers have stated that increased adiponectin is a beneficial effect of exercise on metabolic disorders.[39] The type, volume, intensity of exercise and gender influence adiponectin response.[40, 41]

Significant differences in adipose tissue metabolism between women and men have been reported, with gender as a variable considered in obesity and metabolic disorders.[42] However, the effect of gender on exercise remains unknown.[43] Sex differences in the expression of Aquaporin-7 (AQP7) (associated with genetic predisposition to type 2 diabetes) in women's subcutaneous fat in response to exercise.[44] There was no difference in the results of methyltetrahydrofolate (MTHFR) epigenetic pattern analysis in sex,[45] confirming that further studies are needed to investigate the effect of sex. Regulation of adipose inflammatory response by exercise found a decrease in the expression of adiponectin and TNF-α in both sexes. Only leptin decreased in women after anaerobic exercise.[46] A 2018 meta-analysis review showed aerobic exercise increased adiponectin and decreased leptin levels in diabetic adults, but gender comparisons were absent.[47] In addition, recent research suggests the impact of exercise on inflammatory adipokines may not differ significantly between men and women.[48]

Conclusion

Decreased adipose tissue hypertrophy, decreased TNF-α expression and decreased DPP4 were found in obese rats who exercised compared to obese rats who did not exercise, but these decreases were not statistically significant. Aerobic and anaerobic exercise increases adiponectin and decreases leptin levels in obesity. Further research needs to be conducted to optimally affect inflammation and adipokine in obesity by considering longer durations and types of exercise.

Ethics

All animal care and experimental procedures were approved by the Health Research Ethics Commission of Dr Moewardi Regional General Hospital, decision No: 845/VI/HREC/2022, dated 23 June 2022.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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