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Alterations in PGC-1α and UCP1 Gene Expression in Epicardial Aadipose Tissue and Serum Orexin-A Following Aerobic Exercise in High-Fat Diet Induced Obesity of Male Wistar Rats

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ABSTRACT

BACKGROUND AND OBJECTIVE: Due to the proximity of epicardial adipose tissue (EAT) to the myocardial tissue, it is considered that EAT be more pathogenic than subcutaneous adipose tissue. The aim of this study was to evaluate the alterations of PGC-1α andUCP1 gene expression in EAT and orexin-A following aerobic exercise in high-fat diet induced and obese male wistar rats.

METHODS: In this study, 32 male wistar rats aged 6-week and weight of 180-200 g, assigned randomly in: 1) Normal fat diet (NFD), 2) High-fat diet induced obesity (HFDO), 3) Normal fat diet after high-fat diet induced obesity group (HFDO-NFD) and Aerobic exercise group with normal fat diet after high-fat diet induced obesity group (HFDO-AEX). After obesity-induced in HFDO group (8-week diet with 60% fat) and 48 hours after eight weeks of aerobic exercise (60% of maximal training capacity, 4 sessions/week) in other groups, fasting levels of OXA, Lee index, lipid profile, and gene expression of PGC-1α and UCP1 in EAT have been measured.

FINDINGS: The results revealed that HFD significantly decreased serum OXA, HDL-c, gene expression of PGC1α and UCP1, also caused a significant increase in Lee index, TG, LDL-c, cholesterol and EAT mass ($p \leq 0.001$), but aerobic exercise significantly improved the OXA (34.74%), HDL-c (23.65%), gene expression of PGC-1α and UCP1 (61.28% and 82.67%), lipid profile, EAT mass (76.19%) and Lee index (18.34%) to the normal levels ($P \leq 0.001$).

CONCLUSION: Aerobic exercise by affecting OXA and gene expression of PGC-1α and UCP1 in EAT, probably could reduce the risk factors of cardiovascular diseases due to high-fat diet.

KEY WORDS: *Aerobic exercise, EAT, Obesity, Orexin-A, PGC-1α, UCP1*.

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Introduction

There is currently a global consensus that obesity is a common disease that needs to be treated and, more importantly, needs to be prevented, especially in children and adolescents due to its side effects, mortality from various cardiovascular diseases, and its cost (1,2). Some evidence suggests that topical anti-inflammatory compounds secreted from the epicardial adipose tissue (EAT) play an important role in myocardial muscle function (3). In this regard, the presence of two types of thermogenic brown adipose tissue (BAT) and beige in the body of mammals is very important and there is a lot of evidence that in people with coronary artery disease, the process of differentiating and increasing of BAT in epicardial adipose tissue plays an important role in the development of these diseases (4).

In some meta-analytic studies, the role of additional EAT values in coronary artery occlusion as well as myocardial ischemia has been noted (5,6). On the other hand, one of the most important factors affecting the thermogenic properties of adipose tissue is the neurohormone orexin, which can be changed following exercise (7). In this regard, it is important to change the expression of unpaired type 1 protein (UCP1= Uncoupling protein 1), which is one of the most important thermogenic factors in the mitochondrial inner membrane (8).

Sellayah et al. showed that animals with UCP1 deficiency were more prone to obesity and overweight (9), while PGC-1α (Peroxisome proliferator-activated receptor gamma coactivator 1-alpha) was reported as a PPAR-γ activator, that is an important factor in mitochondrial biogenesis and oxidative metabolism (10) and plays an important role in the thermogenic activity of adipocytes and energy homeostasis by increasing the expression of UCP1 and other thermogenic compounds (11).

Studies on Orexin have focused on how drugs that affect the Orexin system work to treat sleep-wake disorders, drug addiction and appetite, and a few studies on the effects of exercise and the role of Orexin on thermogenic stimuli, especially in EAT, and it seems that increasing the thermogenic characteristics of adipose tissue around the heart and surrounding vessels can be a practical way to reduce EAT and adverse effects of this tissue on heart disease. Therefore, the aim of this study was to investigate the effect of eight weeks of aerobic exercise on serum levels of Orexin-A and gene expression of PGC-1α and UCP1 thermogenic indicators in epicardial adipose tissue of obese males Wistar rats with a high-fat diet.

Methods

Animals: In this experimental study, 32 male Wistar rats with an average weight of 180-200 g and 6 weeks of age were randomly divided into 4 equal groups of 8, including group 1: Normal fat diet (NFD), group 2: High-fat diet induced obesity (HFDO), group 3: Normal fat diet after high-fat diet induced obesity (HFDO-NFD) and group 4: Aerobic exercise group with normal fat diet after high-fat diet induced obesity (HFDO-AEX). This study was performed according to the ethical codes of R.UI.REC. 1396.010, (University of Isfahan). The rats were purchased from Royan Research Institute in Isfahan and kept in triplets in polyethylene cages with dimensions of 20 × 40 × 15 and metal mesh lids in 12 hours of light and 12 hours of darkness (from 7-19) in the range temperatures of 21-24 °C, relative humidity of 50% and free access to water and food.
Diet: After adjusting to induce obesity in animals, a high-fat diet (HFD) was used, including 60% calorie of animal fat, 20% carbohydrate, and 20% protein, which lasted for 8 weeks (12). Then, the animal diet was changed to standard diet for rats (produced by Royan Research Institute of Isfahan), until the end of the research.
Physical composition estimation: Lee index was calculated as an indicator of rodent body composition using the following formula (13).
Lee index= [Weight (g) $^{0.33}$ ÷ the length of the nose to the anus (mm)] × 10^3
Exercise Protocol: In this study, aerobic exercise intervention was an eight-week program (four sessions per week) performed on a rat Motor – Driven Treadmill. Initially, the animals of the training group were trained for 3 days (15 minutes a day at a speed of 20 meters per minute) on 5-line Motor – Driven Treadmill for rodents (made by Danesh-Salar Iranian Company). The maximum training capacity of each animal was determined after 5 minutes of warm-up at a rate of 6 m/min, so that the speed of Motor – Driven Treadmill was increased to 3 m every 3 minutes until the animal reached the fatigue limit (no training continued after 3 electric stimuli), and the maximum speed was recorded as the maximum training capacity (100%) for each animal. The aerobic exercise protocol was performed based on 60% of the average maximum calculated training capacity following a 5-minute warm-up period

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with an average of 30% of maximum speed for 60 minutes or finally the animal reaching fatigue (14). Animals from other groups were also placed on the turned off Motor – Driven Treadmill for a similar period of time to simulate training conditions.

Sampling: Sampling was performed in the HFDO group after obesity and in other groups 48 hours after 8 weeks of aerobic exercise.Blood samples were taken directly from the animal's heart after ether anesthesia, and their serum was isolated and stored at -80° C. In order to sample the EAT, the heart and surrounding adipose tissue were carefully removed from the pericardial space and rinsed with 9% sodium chloride solution and EAT was carefully separated from the heart and both tissues were weighed with a digital scale with an accuracy of 0.0001 g (Mettler Toledo, USA). Then, by dividing the weight of EAT on the weight of the heart, the values were corrected and reported relatively. Subsequently, EAT samples were stored at a volume of one to ten in homogeneous PBS solution at -80° C.

Serum analysis: Blood lipid profile indicators such as TG, HDL-c and LDL were measured by autoanalyzer method using ELISA medical kit made by Pishtaz teb (Iran) with sensitivity of 2 mg / dL and coefficient of in-test changes and coefficient of out-test change less than 2%. Serum Orexin-A was also measured using the ELISA orexin Kit (EL.CSB-E08860) protocol with high specificity and high sensitivity of 3.9 Pg/ml and coefficient of in-test changes and coefficient of out-test change less than 10%.

RNA extraction and gene expression (Real-Time PCR): RNA extraction from EAT was performed using RNA extraction kit (EZ-10 spin column total RNA minipreps super kit) (Canada BIO BASIC INC.), and cDNA synthesis was performed in a completely sterile space under Laminar hood using cDNA synthesis kit (PrimeScript ™ RT reagent Kit) (TaKaRa.Co. Japan) Cat. # RR037A. All steps were performed based on the relevant kit protocol using the PCR device (Australia CG1-96 model, Corbett). To measure changes in the expression of PGC1α, UCP1 and GAPDH (as enteral control) genes, BIO-RAD CFX96 Real-Time PCR was used and by using Table 1 primers, and to calculate changes in gene expression by calculating the ΔCT of desired gene with an internal control gene.

Statistical methods: After ensuring the natural distribution of data using the Shapiro-Wilk test and the equality of variances using the Leven test, in order to examine the intergroup changes, the one-way ANOVA and Tukey post-hoc test, were used and the Pearson correlation coefficient was used to determine the relationship between the variables. The calculations were performed using Excel software version 2016 and SPSS software version 24 and $p<0.05$ was considered significant.

Table 1. Sequence of primers used in research

Gene	F Primer	R Primer	Length
UCP1	5′-GTACCCAGCTGTGCAATGAC-3′	5′-GATGACGTTCCAGGATCCGA-3′	102
PGC- 1α	5′-AAGAGCAAGAAGGCGACACA-3′	5′-CGGGATGGCAACTTCAGTAAT-3	171
GAPDH	5′- TGCTGGTGCTGAGTATGTCGTG-3′	5′- TGCTGACAATCTTGAGGGAGTTG-3′	179

Results

After analyzing the data, the results showed that a high-fat diet significantly reduced serum levels of Orexin-A (18.82%), HDL-c (47.82%) and gene expression of PGC1α and UCP1 thermogenic indicators in EAT tissue (63.6% and 87.43%) and caused significant increase in TG (65.78%), LDL-c (46.47%), total cholesterol (48.67%), relative weight of EAT mass (9.9) 78%) and also the Lee index (23.9%) ($p<0.001$). Weight changes in different groups of animals indicate a significant increase in weight after the transition to aerobic exercise. Performing eight weeks of exercise in the HFDO-AEX group significantly corrected the changes caused by a high-fat diet to return to normal level or even higher level ($p<0.001$) (Figure 1). Following the aerobic exercise course, the values of Orexin-A (34.74%), HDL-c (23.65%) (Figure 2), gene expression of PGC1α and UCP1 thermogenic indicators in EAT tissue increased (61.28% and 82.67%) (Figure 3), but TG levels (49.55%), LDL-c (41.37%), total cholesterol (24.68%), Lee index (-18.34), and the relative weight of the EAT mass (-1.96%) (Figure 2) decreased and corrected to normal levels ($p<0.001$). However, these changes in the HFD-NFD group did not change significantly after entering the normal diet. The correlation coefficient between the levels of Orexin-A and Lee index, the values of thermogenic indices as well as the EAT values showed a significant relationship between serum Orexin-A level and the relative expression of PGC1α and UCP1 genes (Figure A-4). There was also a significant inverse relationship between EAT values and relative expression of PGC1α

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and UCP1 genes (Figure B-4). There was also a significant inverse relationship between serum Orexin-A level and EAT values (Figure D-4) and Lee index (Figure C-4).

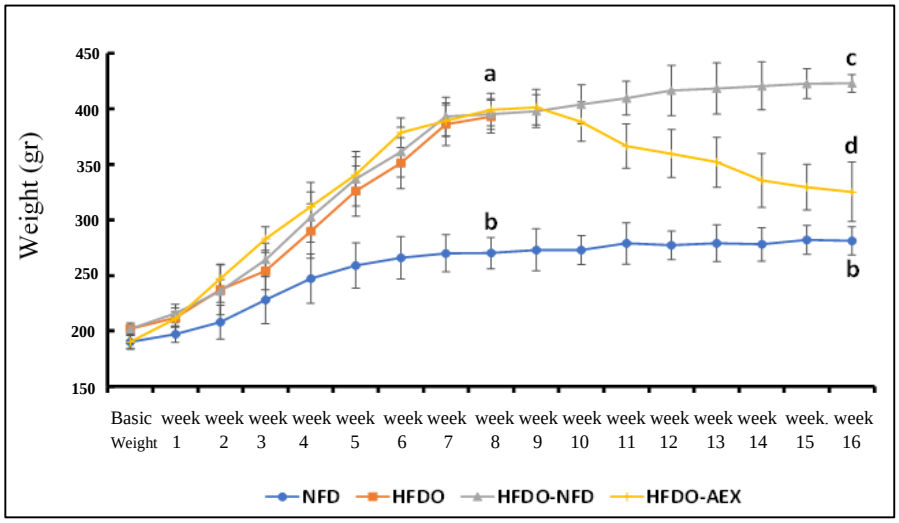

Figure 1. Weight changes of different groups during the research process. Normal fat diet group (NFD), High-fat diet induced obesity group (HFDO), Normal fat diet after high-fat diet induced obesity group (HFDO-NFD) and Aerobic exercise group with normal fat diet after high-fat diet induced obesity group (HFDO-AEX). Dissimilar Latin letters indicate a significant difference and similar Latin letters indicate a non-significant difference between the groups.

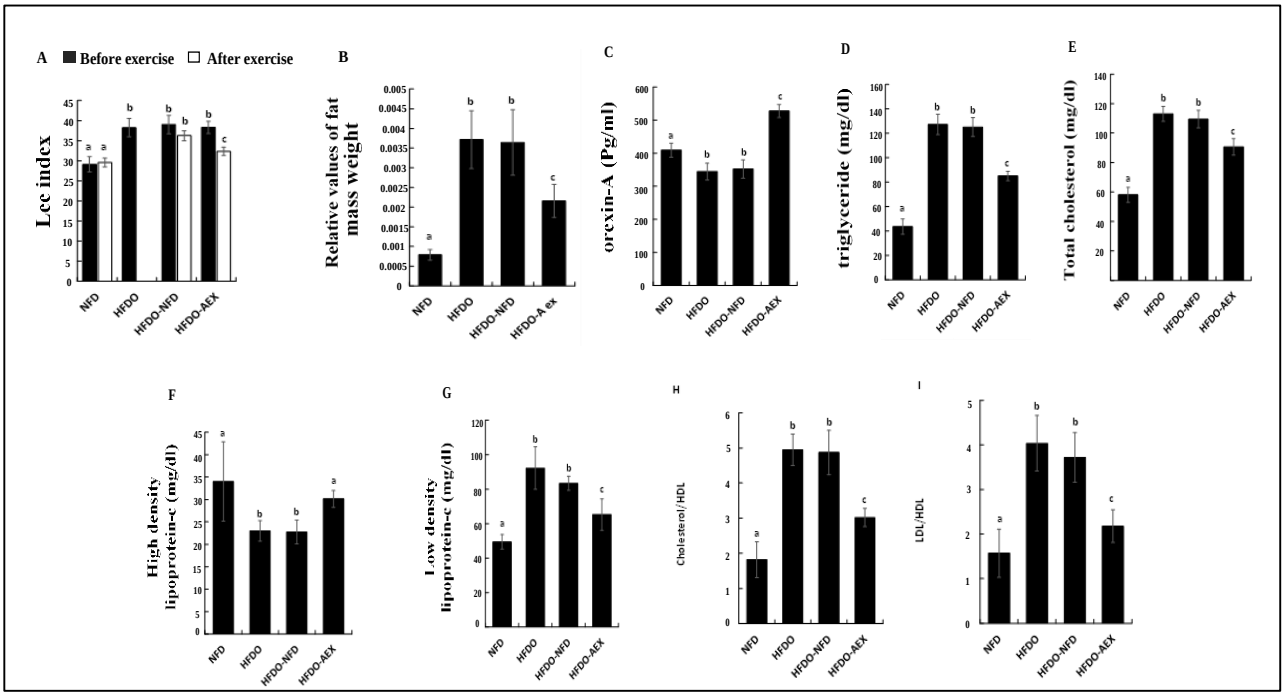

Figure 2. Changes in Lee index (A), epicardial fat mass (B), orexin-A (C), triglyceride (D), cholesterol (E), HDL-c (F), LDL-c (G), CHO / HDL (H), LDL / HDL (I) in different groups. Normal fat diet group (NFD), High-fat diet induced obesity group (HFDO), Normal fat diet after high-fat diet induced obesity group (HFDO-NFD) and Aerobic exercise group with normal fat diet after high-fat diet induced obesity group (HFDO-AEX). Dissimilar Latin letters indicate a significant difference and similar Latin letters indicate a non-significant difference between the groups.

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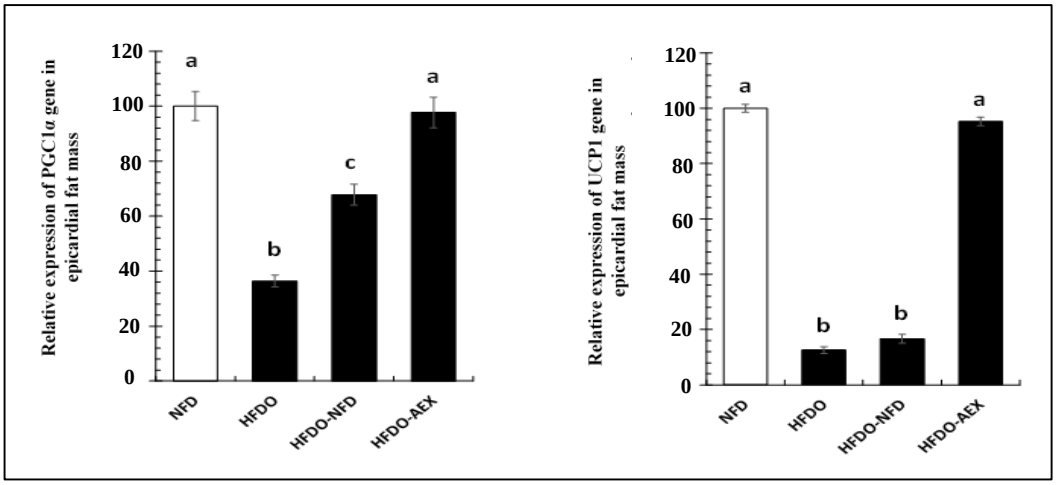

Figure 3. Relative changes in gene expression of PGC1α and UCP1 thermogenic indicators in different groups. Normal fat diet group (NFD), High-fat diet induced obesity group (HFDO), Normal fat diet after high-fat diet induced obesity group (HFDO-NFD) and Aerobic exercise group with normal fat diet after high-fat diet induced obesity group (HFDO-AEX). Dissimilar Latin letters indicate a significant difference and similar Latin letters indicate a non-significant difference between the groups.

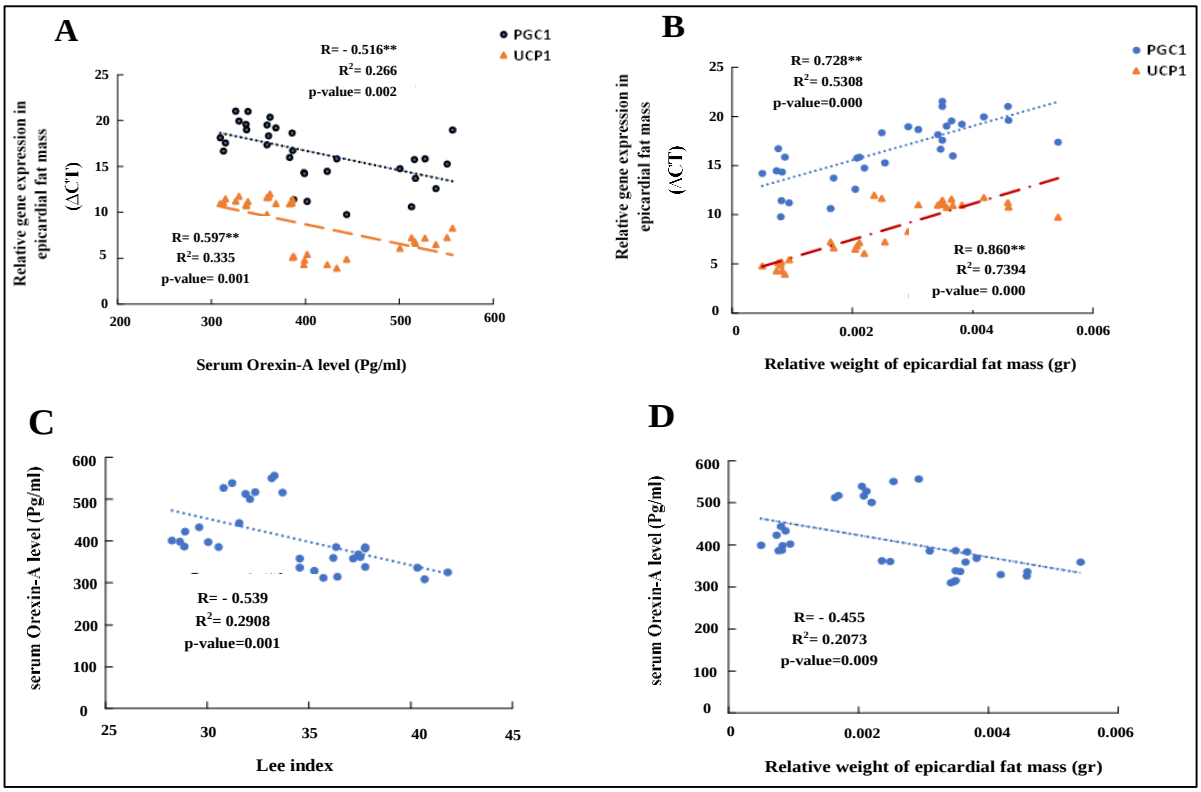

Figure 4. Relationship between relative changes in gene expression of PGC1α and UCP1 thermogenic indices with serum Orexin-A level (A), relative expression of PGC1α and UCP1 genes thermogenic indices with relative weight of epicardial fat mass (B), serum Orexin-A level with Lee index (C) and serum Orexin-A level with a relative weight of epicardial fat tissue (D) (less Delta CT = more relative gene expression).

Discussion

The results of this study showed that aerobic exercise increased serum OXA levels and gene expression of PGC-1α and UCP1 thermogenic indicators of epicardial adipose tissue of rats, which may also reduce the risk factors for cardiovascular disease due to a high-fat diet. In this study, in line with the findings of Iacobellis et al., the Lee index and relative EAT values increased significantly after the

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high-fat diet (15). EAT in people with CAD has been shown to be associated with changes from brown to white, with significant reductions in thermogenic genes (4). In this study, along with the increase in body fat mass and EAT after a high-fat diet, the risk factors for cardiovascular disease increased significantly and the relative expression of thermogenic genes, including PGC1α and UCP1, decreased significantly. Changes in diet and nutrition to normal conditions alone could not prevent this process, and previous studies suggest that excessive calorie intake is a major factor in the differentiation of progenitor cells into white adipocytes in adipose tissue, so changing the phenotype of adipose tissue to store extra calories in these tissues can be one of the reasons for this (11).

In this study, in line with the findings of Hao et al. (16) following a high-fat diet and obesity, serum Orexin-A values were also significantly reduced. Evidence suggests that hyperglycemia and decreased insulin sensitivity due to obesity affect the lateral hypothalamus (Lateral Hypothalamic Area = LHA) affects the Orexin neurons in this area and reduces the expression of the prepro-Orexin gene (17). Another case is that obesity, with its effect on cannabinoid receptors in LHA, inhibits Orexinergic neurons and reduces the secretion of Orexin (18). Previous studies have shown that Orexin neuropeptides are effective in regulating energy expenditure (19).

In this study, along with other findings, there was a significant and inverse relationship between serum Orexin-A levels and EAT values as well as Lee index. Other studies have reported that Orexin-A levels are significantly reduced following obesity (20-22). Studies have shown that both the Orexin system and the obesity process can be affected by exercise (7,23,24). Exercise increases Orexin-A levels in the cerebrospinal fluid (CSF) of rats (25), dogs (26) and humans (16,24,27). The study also found a significant increase in serum Orexin-A levels in obese rats with a high-fat diet following an aerobic exercise program. Aerobic activity is likely to be affected by muscle irisin (28), secretion levels of lactate from muscle during physical activity (16), heart natriuretic peptide (11), changes in CO2 homeostasis (29), glucose metabolism (30) and effect on cannabinoid receptors (18) affect the secretion levels of Orexin in the central nervous system. On the other hand, in addition to tracking Orexin neurons to adipose tissue, the presence of broad Orexin patterns in the brain can be involved in fat tissue metabolism by stimulating other areas of the brain such as the paraventricular nucleus of the hypothalamus (PVN) (31). Previous studies have also shown that stimulation of beta-adrenergic receptors by increasing the regulation of Orexin signals in adipose tissue increases PGC1α expression and stimulates the production of beige adipocytes (11,32). Therefore, due to good innervate to adipose tissue (33), the release of norepinephrine and oroxin is likely to be a strong stimulus for their conversion into thermogenic tissues (11). On the other hand, OXA, through its type 1 receptor, by activating the PLC/P38MAPK pathway in adipose tissue, can alter the expression of downstream genes, such as the expression of PGC-1α and UCP1 genes (34). OXA has also been reported to be associated with energy expenditure due to spontaneous physical activity (SPA), and this neurohormone affected by physical activity, along with changes in tissue thermogenic properties, increases total daily energy expenditure (TDEE) (19,22).

In this study, the expression of PGC1α and UCP1 thermogenic indicators in EAT increased significantly after aerobic exercise. The inverse and significant relationship with EAT values was observed in terms of weight, but there was a significant inverse relationship between Orexin-A levels and Lee index values. On the other hand, there was a significant inverse relationship between EAT weight values with serum Orexin-A levels, which probably confirms the direct relationship between serum Orexin-A levels and the relative expression of PGC1α and UCP1 genes in EAT. Contrary to the findings of this study, in some reports, the administration of Orexin- A in the posterior ventricular hypothalamus (PVH) did not affect the expression of the UCP1 gene (35), while in some other reports 12 weeks of aerobic exercise in young subjects mRNA levels of UCP1 and PGC1α in adipose tissue increased (36).

To justify this, it is likely that the ambient temperature at which the exercise took place, the body composition of the subjects before exercise, the level of initial readiness of the subjects, the presence of disease and continuous aerobic exercise in reducing fat reserves and changes in white adipose tissue and gene expression thermogenic indicators may play a role, although the genetic characteristics of subjects are also important in response to these types of stimuli (37,38). Therefore, according to the findings of this study, it can be stated that aerobic exercise with its potential effect on Orexin neurons can be combined with other complex mechanisms such as changing the expression of

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thermogenic genes in changing the phenotype of adipose tissue from white to brown or beige and turn them into thermogenic tissues are especially effective in EAT. Therefore, continuous aerobic exercise can be independent of nutritional aspects as a practical way to reduce EAT mass and improve the risk factors for cardiovascular disease associated with obesity and high-fat diets.

Conflict of interest: The authors of this article state that there is no conflict of interest regarding the publication of this article.

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