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RESEARCH

Effects of high calorie dietary nutrition and exercise on energy metabolism parameters in obese Wistar albino rats

Obez Wistar albino sıçanlarda yüksek kalorili diyet ve egzersizin enerji metabolizma parametreleri üzerindeki etkileri

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Abstract

Purpose: With the increasing prevalence of metabolic disorders, studies on energy metabolism have advanced, leading to the recent identification of new members in energy metabolism. This study aims to demonstrate the effects of a high-calorie diet and exercise on the newly identified peptides asprosin, irisin, nesfatin-1, and preptin, whose effects on metabolism are still under investigation, and to provide information for future research.

Materials and Methods: In this study, 24 rats were divided into four groups: control, exercise, high-calorie diet, and high-calorie diet with exercise. Serum levels of asprosin, irisin, preptin, nesfatin-1, and insulin were measured using the ELISA method. Additionally, serum levels of glucose, triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were determined by the colorimetric method.

Results: Compared to the control group, there were significant increases in body mass index, glucose, asprosin, TG, TC, and LDL-C levels. Serum HDL-C levels were notably lower in the experimental group compared to the control group. In the exercise group, irisin and nesfatin-1 levels significantly increased, accompanied by reductions in LDL-C, TG, TC, glucose, and preptin levels.

Conclusion: A high-calorie diet was associated with an unfavorable lipid profile, while exercise-induced alterations in the secretion of peptides derived from adipose tissue and/or regulating energy metabolism. Although physical activity emerges as a crucial factor in peptide secretion and maintaining biochemical balance, further research is imperative to comprehensively understand the underlying mechanisms.

Keywords: Asprosin, irisin, nesfatin-1, preptin, exercise

Öz

Amaç: Metabolik hastalıkların artmasıyla birlikte enerji metabolizması çalışmaları da ilerlemiş ve yakın zamanda yeni enerji metabolizması üyeleri tanımlanmıştır. Çalışmanın amacı, yüksek kalorili diyet ve egzersizin yeni tanımlanan ve metabolizma üzerindeki etkileri halen araştırılan asprosin, irisin, nesfatin-1 ve preptin peptidleri üzerindeki etkilerini göstermek ve gelecekteki araştırmalar için katkı sağlamaktır.

Gereç ve Yöntem: Bu çalışmada 24 sıçan kontrol grubu, egzersiz grubu, yüksek kalorili diyet grubu ve yüksek kalorili diyet ve egzersiz grubu olmak üzere 4 gruba ayrıldı. Serum asprosin, irisin preptin, nesfatin-1 insülin düzeyleri ELISA yöntemi ile ölçüldü. Serum glukoz, trigliserit (TG), total kolesterol (TK), yüksek yoğunluklu lipoprotein kolesterol (HDL-C) ve düşük yoğunluklu lipoprotein kolesterol (LDL-C) düzeyleri kolorimetrik yöntemle belirlendi.

Bulgular: Kontrol grubuna kıyasla, vücut kitle indeksi, glukoz, asprosin, TG, TC ve LDL-C seviyeleri önemli ölçüde arttı. Deney grubu ile kontrol grubu arasında serum HDL-C seviyeleri belirgin bir şekilde daha düşüktü. Egzersiz grubunda irisin ve nesfatin-1 seviyeleri önemli ölçüde artarken, LDL-C, TG, TC ve glukoz ve preptin seviyelerinde azalma görüldü.

Sonuç: Yüksek kalorili diyet, olumsuz bir lipid profili ile ilişkilendirildi. Egzersiz, genellikle yağ dokusundan türeyen ve/veya enerji metabolizmasını düzenleyen peptitlerin salınımında değişikliklere neden oldu. Fiziksel aktivite, peptit salınımında ve böylece biyokimyasal dengeyi sürdürmede önemli bir faktör olarak ortaya çıksa da mekanizmayı daha net anlamak için daha fazla araştırmaya ihtiyaç vardır.

Anahtar kelimeler: Asprosin, irisin, nesfatin-1, preptin, egzersiz

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INTRODUCTION

Recent studies on obesity have concentrated on various appetite hormones that play a crucial role in metabolism and body fat distribution[1]. The hypothalamus features two distinct pathways for regulating food intake and energy metabolism. In the presence of sufficient energy, it curtails food intake and triggers the release of anorexigenic peptides from peripheral tissues, such as nesfatin and leptin, fostering a sense of satiety. Conversely, in the case of energy deficiency, it induces a feeling of hunger and secretes orexigenic peptides like preptin and asprosin[2]. Current studies have focused on investigating the role of various recently discovered adipokines, such as asprosin, preptin, nesfatin-1, and irisin, in regulating fat and glucose metabolisms[3-7].

In the study of Romere et al.[4], it was stated that asprosin is an orexigenic hormone that increases appetite and ultimately leads to obesity and weight gain[4,8]. Duerrschmid et al.[8] stated that circulating asprosin crosses the blood-brain barrier and directly activates orexigenic AgRP+ neurons through a cAMP-dependent mechanism, resulting in appetite stimulation. This mechanism leads to the inhibition of downstream anorexigenic proopiomelanocortin (POMC)-positive neurons[8].

Nesfatin-1 is a potent anorexigenic peptide with a molecular weight of 9.7 kDa, consisting of 82 amino acids, and was discovered by Oh et al. in 2006[5]. It is involved in the regulation of homeostatic nutrition. Nesfatin-1 is an amino-terminal fragment derived from NEFA/nucleobindin2 (NUCB2), a protein involved in appetite control. NUCB2 consists of a total of 396 amino acids, including a 24-amino acid signal peptide[5].

Preptin is a polypeptide hormone composed of 34 amino acids, released from the β-cells of the pancreas, and was discovered by Buchanan et al.[6] Studies have indicated higher levels of plasma preptin in patients with type 2 diabetes mellitus (T2DM)[6,9]. This peptide has been reported to increase the secretion of proinsulin-like growth factor II, thereby enhancing insulin secretion[6].

Irisin, identified by Böstrom et al. in 2012, is a recently discovered hormone weighing 12.587 kDa and comprising 112 amino acids. It is released not only from myocytes but also from adipose tissue, playing a crucial role in converting white adipose tissue into brown adipose tissue. This hormone, irisin, facilitates the beneficial impacts of exercise on metabolism. It has been detected in various body tissues, including adipose tissue, heart muscle, cerebrospinal fluid, human breast milk, saliva, and Purkinje cells in the cerebellum[7]. By influencing adipose tissue metabolism and contributing to glucose homeostasis, irisin acts as an anti-diabetic and anti-obesity hormone[3,7].

Sedentary behavior and a high-calorie diet can contribute to the development of various diseases, adversely affecting the quality of life. In response to this, researchers are exploring novel diagnostic and therapeutic approaches. Our objective was to monitor the behavior of specific peptides under the influence of dietary and exercise conditions, simultaneously evaluating other biochemical parameters. This investigation aimed to ascertain whether these recently discovered peptides, which currently lack sufficient evidence, could potentially be utilized for therapeutic purposes or serve as biomarkers in the future.

MATERIALS AND METHODS

The study, approved by Çanakkale Onsekiz Mart University Animal Experiments Local Ethics Committee under the decision ÇOMÜ HADYEK 20.04.2020; with the code number 2020/04-08, was conducted in the laboratories of Çanakkale Onsekiz Mart University Health Services Vocational School and the Laboratory of Experimental Animals Research and Application. The procedure was followed by researchers with a Laboratory Animal Use Certificate.

Diets and experimental design

Twenty-four female rats were divided into four groups, each consisting of six rats. The groups were designated as the Control group, Exercise group (E), High-calorie Diet group (HC), and High-calorie Diet + Exercise group (HC+E). The HC groups were provided with a diet comprising 4000 kcal rat chow and 20% high-fructose corn syrup throughout the experiment[10]. Groups fed with the standard diet were provided with 2400 kcal rat chow. Body Mass Index (BMI) values were calculated based on the Lee scale (Body weight kg/nose to anus length 3x100). The physical conditions of the working environment were maintained at a temperature of 21 ± 2°C, with a

humidity level of 50% ± 5%, and a 12-hour light and 12-hour darkness cycle.

Exercise program

The E and HC+E groups underwent a 30-minute exercise program in a 100 cm x 100 cm tank with water maintained at 32-37°C and positioned at a height of 85 cm. The study applied the swimming protocol of Claudio et al. with some modifications[11]. The 4-week swimming exercise concluded with a 48-hour rest period.

Blood collection and biochemical analysis

After a 12-hour fasting, blood samples were collected from rats' hearts via puncturing and these samples were transferred to tubes without anticoagulant for serum. After the tubes were centrifuged at 1400 g and 4°C with Nüve NF 1200 centrifuge for 10 minutes, the serum was separated and stored in labeled tubes at -80°C.

In the study, it was treated with nesfatin-1 (Elabscience Biotech Co. Ltd, USA, Catalog no: E-EL-R2514), irisin (Elabscience Biotech Co. Ltd, USA, Catalog no: E-EL-R2625), preptin (BT-Lab, Shanghai-China Catalog no: E1516Ra), insulin (Elabscience Biotech Co. Ltd, USA, Catalog no: E-EL-R3034), asprosin (BT-Lab, Shanghai-China, Catalog no: E1703Ra).

Commercial kits using the sandwich ELISA technique were measured. Glucose (Rel Assay Diagnostics kits, Mega Tıp, Gaziantep, Türkiye, Catalog no: RLB252), triglyceride (TG) (Rel Assay Diagnostics kits, Mega Tıp, Gaziantep, Türkiye, Catalog no: RLB257), total cholesterol (TC) (Rel Assay Diagnostics kits, Mega Tıp, Gaziantep, Türkiye, Catalog no: RLB248), high-density lipoprotein cholesterol (HDL-C) (Rel Assay Diagnostics kits, Mega Tıp, Gaziantep, Türkiye, Catalog no: RLB261) and low-density lipoprotein cholesterol (LDL-C) (Rel Assay Diagnostics kits, Mega Tıp, Gaziantep, Türkiye, Catalog no: RLB263) was studied with commercial kits using a colorimetric measurement technique. Mindray-bs300 model fully automatic biochemistry analyzer, Bio-Tek ELx800 Elisa reader, and Bio-Tek ELx50 washer were used in the study.

Statistical analysis

The data were analyzed using GraphPad Prism 8 software. The homogeneity of the data was assessed using the Levene test. Subsequently, a one-way analysis of variance (ANOVA) was performed to determine potential differences among the groups. Significance was determined with a P-value of less than 0.05 ($P < 0.05$). Differences between groups were evaluated using the Tukey post hoc test. The evaluation was conducted using mean and standard deviation values ($\bar{X} \pm$ SD).

RESULTS

Table 1 shows BMI, glucose, and insulin values. The study revealed a significant decrease in BMI and glucose in the HC-E group ($P<0.001$). Additionally, a decrease in glucose levels was observed in the E group compared to the control group ($P<0.001$). In the comparison between the E group and the control group, there was a significant increase in insulin values ($p<0.05$).

Table1. BMI and Serum Glucose, Insulin levels.

Parameters	Control $\bar{X} \pm$ SD	Exercise $\bar{X} \pm$ SD	High-Calorie Diet $\bar{X} \pm$ SD	High-Calorie Diet+Exercise $\bar{X} \pm$ SD	P-value
BMI	26.02 ± 0.24	27.18 ± 0.3*	30.56 ± 0.29*	27.4 ± 0.16*	P <0.001
Glucose (mg/ dL)	215 ± 5.9	109 ± 14.8	296 ± 21.94*	241 ± 25.56*	P <0.001
Insulin (ng/ mL)	0.09 ± 0.012	0.25 ±0.013*	0.10 ± 0.04	0.14 ± 0.02*	P <0.05

"*" indicates a statistical difference compared to the control group.

Table 2 shows serum TC, TG, HDL-C, and LDL-C values. No statistically significant difference was found in TG values between the control group and group E; however, a significant increase was noted in TG values for groups HC and HC-E compared to the control group ($P<0.001$). Lower TG values were observed in group HC-E compared to group HC ($P<0.001$). Regarding TC values, a significant difference was observed in group HC compared to the control group ($P<0.001$).

When HDL-C analysis was examined, group HC showed a statistically significant difference from both the control group and group HC-E (P<0.05). However, the difference between the control group and groups E and HC-E was insignificant. In LDL-C analysis, there was no significant difference between the control group and the treatment groups; however, there was a significant increase in groups HC and HC-E compared to group E (P<0.001).

Table 2. Serum TG, TC, HDL-C, LDL-C levels.

Parameters	Control $\bar{X} \pm SD$	Exercise $\bar{X} \pm SD$	High-Calorie Diet $\bar{X} \pm SD$	High-Calorie Diet+Exercise $\bar{X} \pm SD$	P-value
TG (mg/ dL)	36.07 ± 5.23	30.38 ± 4.76	82.13 ± 7.05*	57.43 ± 2.83*	P <0.001
TC (mg/ dL)	74.08 ± 2.82	67.13 ± 4.9*	87.1 ± 3.4	83.51 ± 1.7	P <0.001
HDL-C (mg/ dL)	52.27 ± 3.01	48.7 ± 1.0	47.18 ± 2.9*	51.72 ± 2.62	P <0.05
LDL-C (mg/ dL)	14.50 ± 2.62	10.68 ± 2.68	19.23 ± 4.03*	18.45 ± 1.83*	P <0.001

"*" indicates a statistical difference compared to the control group. Triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C).

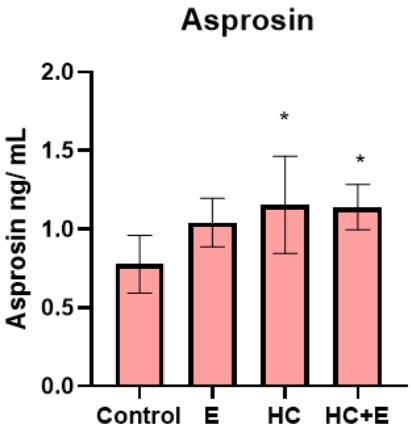

Figure 1. Blood serum asprosin (ng/ mL) "*" indicates a statistical difference compared to the control group.

The group names were abbreviated as follows; Control group, Exercise group (E), High-Calorie Diet group (HC), High-Calorie Diet+Exercise group (HC+E), (P<0.05, $\bar{X} \pm SD$).

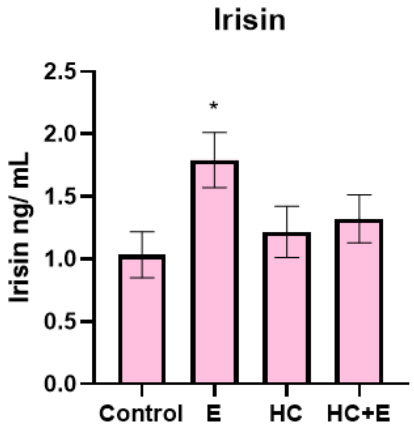

Figure 2. Blood serum irisin (ng/ mL) "*" indicates a statistical difference compared to the control group.

The group names were abbreviated as follows; Control group, Exercise group (E), High-Calorie Diet group (HC), High-Calorie Diet+Exercise group (HC+E), (P<0.05, $\bar{X} \pm SD$).

Figure 1 shows serum asprosin values. When asprosin values were evaluated between the groups, a significant difference was found between the control group and groups HC and HC-E (P<0.05). Although there was a numerical increase in the exercise group, this difference was not significant.

Figure 2 shows serum irisin values. When irisin values were examined between the groups, a statistical difference was found between group E and all other groups (P<0.05). Although there was a numerical increase between the control group and groups HC and HC-E, there was no statistical difference between them.

Figure 3 shows serum nesfatin-1 values. In this study, the concentration of serum nesfatin-1 decreased in group HC compared to the control group and increased in group E (P<0.05). Figure 4 shows serum preptin values. A significant decrease in serum preptin levels was observed in group HC (P<0.05). Although there was a numerical increase in groups HC-E and E compared to the control group, this was not statistically significant.

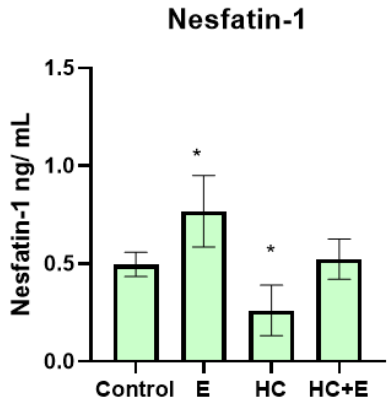

Figure 3. Blood serum nesfatin-1 (ng/ mL) "*" indicates a statistical difference compared to the control group.

The group names were abbreviated as follows; Control group, Exercise group (E), High-Calorie Diet group (HC), High-Calorie Diet+Exercise group (HC+E), ($P<0.05$, $\bar{X} \pm SD$).

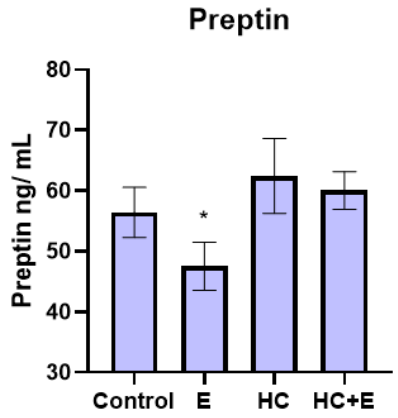

Figure 4. Blood serum preptin (ng/ mL) "*" indicates a statistical difference compared to the control group.

The group names were abbreviated as follows; Control group, Exercise group (E), High-Calorie Diet group (HC), High-Calorie Diet+Exercise group (HC+E), ($P<0.05$, $\bar{X} \pm SD$).

DISCUSSION

As obesity becomes an increasingly prevalent health issue, research on prevention and treatment has gained importance in recent years. Monitoring changes in metabolism members, especially during the obesity process, will contribute to future treatment approaches. To achieve this, some studies have been conducted to observe the alterations in new energy metabolism members in response to nutrition and/or exercise.

Asprosin is an orexigenic hormone whose concentration increases during fasting and falls with fullness[8,12]. Blood glucose levels are elevated and asprosin levels have also been shown to rise in circumstances like obesity and diabetes[4]. Asprosin is said to be expressed in a variety of tissues and is mostly released by adipose tissues[13,14,15]. Asprosin induces the liver to release glucose[14]. Exercise and a healthy eating plan will help to regulate asprosin production and, in turn, glucose secretion[16]. According to Hekim et al. (2002), asprosin may stimulate the liver's release of glucose as the cause [17]. Studies linking exercise to a decrease in asprosin stress that the type and amount of exercise can have an impact. In their study, Pirani et al. (2022) found that following two distinct training sessions, the expression of the asprosin and FBN1 genes dropped[16]. According to studies, exercise can help control body weight and cholesterol profile[18]. In a different study, it was noted that the concentration of asprosin dropped in groups engaging in continuous swimming training. One study reported an increase in asprosin levels 60 minutes after exercise, followed by a reduction 3 minutes after exercise[19].

A study by Sünnetçi et al.[20] indicates that obese children exhibit higher circulating levels of asprosin compared to children of normal weight. Additionally, Lu et al.'s research (2023) underscores the negative effects of elevated asprosin levels in obesity, demonstrating that these levels induce endothelial dysfunction and are mitigated through asprosin neutralization[21]. Emre et al. (2023) further suggest that metabolic disorders resulting from oxidative stress lead to an increase in blood asprosin levels[21]. According to a study by Romere et al.[4], patients with type 2 diabetes and obesity have higher levels of asprosin. Evaluating asprosin in conjunction with adipokines possessing both similar and dissimilar qualities is crucial for a more comprehensive understanding of its working mechanism. In this study, compared to the control group, asprosin levels increased in the HC and HC-E groups, but a decrease was observed in the HC-E group, thought to be the result of exercise.

Oh-i et al.[5] reported that the injection of nesfatin-1 reduced food intake, and the application of an antibody-neutralizing nesfatin-1 led to a decrease in the appetite ratio stimulated by nesfatin-1. Based on this information, they concluded that nesfatin-1 is an anorexigenic peptide[5]. The circulating level of nesfatin-1 increases after eating and decreases during hunger; therefore, this peptide is considered an appetite-suppressant factor contributing to a reduction in BMI. Additionally, it has been reported that nesfatin-1 affects the circulatory lipid profile in addition to its anti-hyperglycemic effect[22].

In a study with obese women, it was reported that exercise increases nesfatin-1, functioning as a trigger for satiety[23]. Individuals on a high-calorie diet showed a decrease in nesfatin-1 levels, while those trying to lose weight through exercise exhibited high levels of nesfatin-1[23]. A study on the variation of nesfatin-1 and irisin with exercise in football-playing athletes at three different times showed an increase in irisin levels, while nesfatin-1 levels decreased in all participants[24]. In rats engaged in aerobic activity, the expression levels of the nesfatin-1 gene were found to be significantly high. The studies listed above indicate that the type and even the duration of exercise may have an impact on the peptide[25].

In this study, groups following a high-calorie diet exhibited high levels of blood glucose, total cholesterol (TC), triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C). Nesfatin-1 ratios decreased, but a significant increase was observed with exercise. This suggests that the peptide is not only a satiety-inducing factor but may also be closely associated with exercise. Irisin is a myokine described by Bostöm et al.[7] It is also reportedly effective on skeletal muscle and adipose tissue by transforming white adipose tissue into brown adipose tissue[26]. It was reported that swimming exercise decreases body weight and increases irisin levels[27]. Despite the vast amount of literature on the connection of irisin with exercise, there is no consensus on the reason for their connection. Studies claiming that serum irisin levels decrease after exercise explained this connection by the fact that exercise stimulates the mechanism activating gluconeogenesis and increases the expression of GLU-4 mRNA, which in turn increases glucose use further in response to resulting hypoglycemia, leading to decreased irisin levels[28]. Bostöm et al.[7] reported that irisin is exercise-induced and increased irisin levels cause increased energy expenditure in mice without any change in movement or food intake. Another study suggested that asprosin levels increased in male rats after irisin administration, but this effect could not be seen at the same level in female rats, and it was noted that gender made a difference in the secretion of irisin. LDL-C and TG values, which increased in obesity, decreased after administration of irisin. Researchers emphasized that irisin is also effective in curing obesity but does not change asprosin levels[3]. According to Vliora et al. (2022), irisin influences lipolysis and mitochondrial respiration in a time-dependent way, suggesting that it might be a therapeutic target for the treatment of obesity[29]. A study discussed whether irisin is considered an exercise hormone or a transmembrane receptor and evaluated the inadequacy of existing techniques for irisin measurement, which may be the main reason for conflicting statements regarding irisin. Therefore, it is stated that there is a need for the development of advanced techniques for irisin analysis[2,30]. In this study, TG and LDL-C, HDL-C, and TC levels were also decreased in the exercise groups with increased irisin levels compared to the control group. These results correlate favorably with previous studies which reported high values of BMI, TG, and TC for group HC but lower values for group HC-E because of exercise. Such a decline in the lipid profile and decreased BMI have been attributed to exercise and energy expenditure. Irisin, known as the exercise hormone, is secreted from both muscle and adipose tissue, playing a remarkable regulatory role in energy metabolism. Therefore, the fact that it might be a regulator for blood lipid profiles and blood glucose, and thus have therapeutic effects on diabetes and obesity, as well as spontaneously increasing with exercise, supports the positive effects of exercise.

It stimulates insulin release from pancreatic β cells. Preptin injection has been reported to stimulate and increase glucose-dependent insulin secretion using a concentration-dependent mechanism. The fusion of anti-preptin immunoglobulin led to decreased insulin secretion[6]. Thus, the physiological relationship between insulin secretion and preptin was explained. It is argued that insulin is co-secreted with preptin as a pancreatic response to an increased level of glucose in the blood after feeding. In addition, researchers have found high circulating levels of the preptin hormone in the case of obesity[31]. Another study reported a positive relationship between preptin concentration fasting insulin levels and blood glucose levels. Moustafa et al.[28] reported that 6 weeks of swimming exercise caused a significant increase in pancreatic preptin mRNA and its receptors, resulting

in a significant increase in preptin mRNA in the liver. According to one study, diabetic individuals exhibited higher levels of preptin, insulin, and the lipid profile than those in the control group[32]. In this study, glucose, insulin, and preptin values decreased in the exercise groups, and increased in group HC. Despite this decline with exercise in group HC-E, this decline was not significant. These results were found to be consistent with the literature.

The study has certain limitations. Evaluating the molecular expressions of these peptides in different tissues would provide more detailed information to illuminate the mechanism for a better assessment of the results.

Based on the data reported in this study, it can be concluded that exercise affects irisin, nesfatin-1, and preptin. It was observed that the respective peptides consistently influenced each other under similar conditions, suggesting that these peptides might be operating through a common mechanism. Further studies employing advanced techniques are needed to understand this complex mechanism influenced by diet, gender, exercise type, and exercise duration.

Author Contributions: Concept/Design : SÇ; Data acquisition: YD, SÇ; Data analysis and interpretation: YD, SÇ; Drafting manuscript: YD, SÇ; Critical revision of manuscript: YD, SÇ; Final approval and accountability: SÇ, YD; Technical or material support: YD, SÇ; Supervision: YD, SÇ; Securing funding (if available): n/a.
Ethical Approval: The study was approved by Çanakkale Onsekiz Mart University Animal Experiments Local Ethics Committee with the decision of ÇOMÜ HADYEK 20.04.2020; 2020/04-08 code number.
Peer-review: Externally peer-reviewed.
Conflict of Interest: None of the authors disclosed any conflicts of interest.
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