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The Effect of Long-Term Exercise Training with Omega-3 Fatty Acid Supplement on Serum Iris and Some Blood Parameters

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ABSTRACT

This research; the effects of omega-3 fatty acids and exercise on irisin, leptin and ghrelin hormone total cholesterol, HDL, LDL and triglyceride levels when applied separately or in combination were investigated. Method; A total of 28 male Wistar albino rats, 8 weeks old, were randomly divided into 4 groups of seven each as control, exercise, omega (400 mg/kg) and exercise + omega-3. After starting the omega-3 fatty acid diet, rats were subjected to a 20-minute jog test 5 days a week for 10 weeks. Results; It was determined that exercise and omega-3 supplementation decreased the total cholesterol level in the groups in which they were applied separately, and increased the total cholesterol level when they were applied together. When we examined the triglyceride levels, it was determined that while there was an increase in the exercise group, there was a decrease in the omega group, and when the exercise and omega-3 supplementation were combined, it decreased similarly to the omega group. In addition, when we examined HDL and LDL cholesterol levels, it was found that exercise and omega-3 fatty acids increased HDL levels separately and in combination, LDL levels decreased in omega-3 and exercise groups, but there was no change in cholesterol levels. Conclusion; positive effects of exercise on lipid profile and iris, moderate positive correlation between irisin and leptin; It can be said that irisin and ghrelin show a highly positive relationship and omega-3 fatty acids have positive effects on the lipid profile.

Key words: irisin, exercise, omega-3 fatty acid, lipid profile

1. INTRODUCTİON

According to the World Health Organization (WHO), excess weight and obesity are caused by the imbalance between the energy taken into the body and the energy consumed, and the body fat mass increases compared to the lean body mass, and as a result, all organs in the human organism, especially the cardiovascular and endocrine system. It is considered as an important

health problem that can cause various diseases and even death by affecting the (James et al., 2001). It is known that the factors causing obesity have a wide range of effects depending on genetic factors, unhealthy diet, sedentary life, changing eating habits, developments in technology, social and local factors (US Department of Health and Human Services, 2001).

Obesity treatment is a chronic disease that has existed for many years, but the success rate of treatment is insufficient. Although obesity cannot be solved in a short time, treatments such as multidisciplinary (education, diet, exercise, behavioral therapy, drug therapy, surgical treatment) are required throughout life. This multidisciplinary method allows to keep obesity under control, but if treatment is not continued, obesity will recur (Bray, 1993). When we examine the treatment methods of obesity; When surgical treatment methods are applied, it is known that in addition to the risk of developing complications during and after the operation in the obese individual, it also has a negative impact on the country's economy (Paterson, 1971). When we examine the treatment principles used in the treatment of obesity, drugs and surgical methods are not preferred in the first stage because they have negative effects. In the first stage of obesity treatment, the basis of treatment consists of education, behavioral treatment, lifestyle change, diet and exercise (Serter, 2004).

Combined physical activity and low-calorie diet; It provides weight loss, reduction of fat ratio and increase of cardiovascular compliance (Baltacı ve Tedavi, 2008). In the literature, there are studies in which supplementary foods are used for weight loss along with exercise. One of these supplements is the Omega-3 fatty acid component. It is known that omega-3 fatty acids play a role in regulating body weight by providing energy production / oxidation, preventing Cardiovascular Diseases by affecting circulating cholesterol, and modulating membrane phospholipid / fatty acid composition, and as a result diabetes is affected. Omega-3 is said to have an effect on these parameters, but more studies are needed (De Mello et al., 2019).

Based on this information, it is a question of interest what effects exercise will have on irisin hormone levels, which have an effect on weight loss and fat burning, together with omega-3 fatty acid supplementation. Therefore, this study aims to clarify the effects of omega-3 and exercise separately and in combination on weight loss, whether they mediate the change in irisin levels, and in which case, fat burning is higher, and it is important to experts in the exercise programs and diets that will be adapted to people in line with these results. It aims to provide information and advice. In addition, it is aimed to examine the effects of omega-3 fatty acids and exercise on total cholesterol, triglyceride, HDL and LDL levels, both separately and in combination.

2. METHOD

Selection of animals

Male Wistar Albino rats (8 weeks old, 220-350 g body weight) were obtained and used in this experimental study from Van Yüzüncü Yıl University Experimental Research and Application Center. Rats were maintained in a standard laboratory environment (temperature: 22 ± 2 °C, relative humidity: 55 ± 5% and 12/12 hour light/dark cycle). The experiment was carried out at Van Yüzüncü Yıl University Experimental Research and Application Center. This study was approved by Van Yüzüncü Yıl University Animal Experiments Local Ethics Committee (Protocol No: 2021/02-12 Date: 25/02/2021) by Van Yüzüncü Yıl University Scientific Research Projects Coordination Unit with the number TYL-2021-9497. supported as a project. All experiments were performed in accordance with internationally accepted standard ethical guidelines for the use and care of laboratory animals, as described in European community guidelines (EEC Directive 86/609/EEC of 24 November 1986).

Experiment Design

Power analysis was carried out in order to generalize the results obtained for the assignment of the experimental groups and to obtain a sufficient number of samples. The power analysis resulted in groups of 7 members each. Twenty-eight male Wistar albino rats (8 weeks old, 220-350 g body weight) were included in the study. This study consists of four different experimental groups (n=7 for each group).

Group I (Control Group): No supplement or exercise was applied.

Group II (Exercise Group): A long-term exercise program was applied for 8 weeks.

Group III (Supplement Group): Omega-3 supplementation was applied regularly for 8 weeks.

Group IV (Supplementation + Exercise Group): Omega-3 supplement was applied with long-term exercise for 8 weeks.

Treadmill Exercise Program

The rats in the exercise group were exercised on a special treadmill 5 days a week for eight weeks. The rats subjected to exercise were started to run at a speed of 5 m/min at the beginning on the (MAY-TME 0804, Commat Limited) brand treadmill and exercise was applied for 2 weeks, 5-10 minutes daily, before the exercise protocol to ensure adaptation to the exercise. At the end of the 2-

week adaptation period, the rats were run at a speed of 15 m/min for 20 minutes on the exercise days. Exercise practices were carried out continuously between 08:00 and 10:00.

Omega-3 Fatty Acid Supplement

After the rats were divided into groups, the commercially available Omega-3 fatty acid component was administered to the rats at a daily rate of 400 mg/kg in the groups that would receive Omega-3 supplementation. Omega-3 fatty acid component provided in liquid form was administered to each rat by oral gavage method.

Biochemical Analysis

At the end of the eight-week study, the rats were decapitated in a sterile environment and 5 ml of blood was collected by intracardiac method. Blood samples were taken into tubes containing aprotinin and centrifuged at 4,000 rpm for 10 minutes to separate the serum. The contents were transferred to pre-assigned and numbered Eppendorf tubes and stored at -80°C until analysis. Afterwards, it was studied in an autoanalyzer to measure the biochemical parameters in the serum samples obtained.

The irisin levels in the samples obtained were determined by ELISA method. The measurement range of the rat irisin ELISA kit was 0.25-72 ng/mL, the sensitivity was 0.247 ng/mL, Intra-Assay: CV<10%, Intra-Assay: CV<12%. Bio-Tek ELX50 washer (BioTek Instruments, USA) at Yüzüncü Yıl University Faculty of Medicine was used for plate washings. In absorbance readings, a BIOTEK-ELx800 reader (BioTek Instruments, USA) brand device was used and the test results were calculated according to the standard curve created using standard values, and the results were measured as ng/mL.

Statistical Analysis

According to the data we obtained, after the shapiro-wilk test was applied for the test of normality and homogeneity, one-way anova test, which is one of the parametric tests, was applied ($p<0.05$ was considered a statistically significant difference). Tukey was used in the post hoc analysis to determine the difference between the groups. Data were analyzed using SPSS-21 statistical package program. Significance was accepted as $p<0.05$.

3. RESULTS

Table 1. Mean Lipid Profiles of the Groups.

Parameters	KG ($\bar{x}$± Ss)	EG ($\bar{x}$± Ss)	Omega ($\bar{x}$± Ss)	E+Omega ($\bar{x}$± Ss)
Cholesterol (mg/dL)	56.61±3.12^{a}	43.02±3.13^{c}	51,05±3.50^{b}	58,10±2.25^{a}
Triglyceride (mg/dL)	41.07±3.55^{b}	73.27±3.55^{c}	37,42±2.07^{a}	37,60±9.26^{a}
HDL-C (mg/dL)	13.51±1.29^{a}	15.75±0.51^{b}	15,40±0.40^{b}	16,16±0.90^{b}
LDL-C (mg/dL)	28.02±2.76^{a}	19.03±3.10^{c}	23,12±2.79^{b}	28,02±2.03^{a}

KG: Control Group. EG: Exercise Group. E+Omega: Exercise+Omega group. HDL-C: High-density lipoprotein cholesterol. LDL-C: Low-density lipoprotein cholesterol. abc: There is a statistically significant difference between the groups indicated with different letters on the same line ($p<0.05$).

Table 2. Average Irisin, Leptin and Ghrelin Levels of the Groups.

Parameters	KG ($\underline{X}$± Ss)	EG ($\underline{X}$± Ss)	Omega ($\underline{X}$± Ss)	E+Omega ($\underline{X}$± Ss)
Irisin (mg/dL)	5,68±0,47^{b}	9,64±1,25^{a}	5,51±1,03^{b}	4,60±0,53^{c}
Leptin (mg/dL)	220,35±50,58	235,73±57,71	189,03±34,50	186,15±21,05
Ghrelin (mg/dL)	1190,97±179,91^{b}	1543,11±154,26^{a}	888,69±132,09^{c}	1063,43±174,02^{b}

KG: Control Group. EG: Exercise Group. E+Omega: Exercise+Omega group. abc: There are significant differences between the groups indicated by different letters on the same line.($p<0.05$).

As seen in Table 3, the correlation coefficient value between irisin and leptin was 0.409, showing a moderately positive correlation at the $p<0.05$ level; It was determined that the correlation coefficient value between irisin and ghrelin was .686 and showed a high positive correlation at the $p<0.00$ level.

Table 3. Investigation of the Relationship Between the Mean Irisin, Leptin and Ghrelin Levels of the Groups

Parameters		Leptin (mg/dL)	Ghrelin (mg/dL)
İrisin (mg/dL)	r	0,409	,686
	p	0,031	0,000

*p<0.05. **p<0.00.

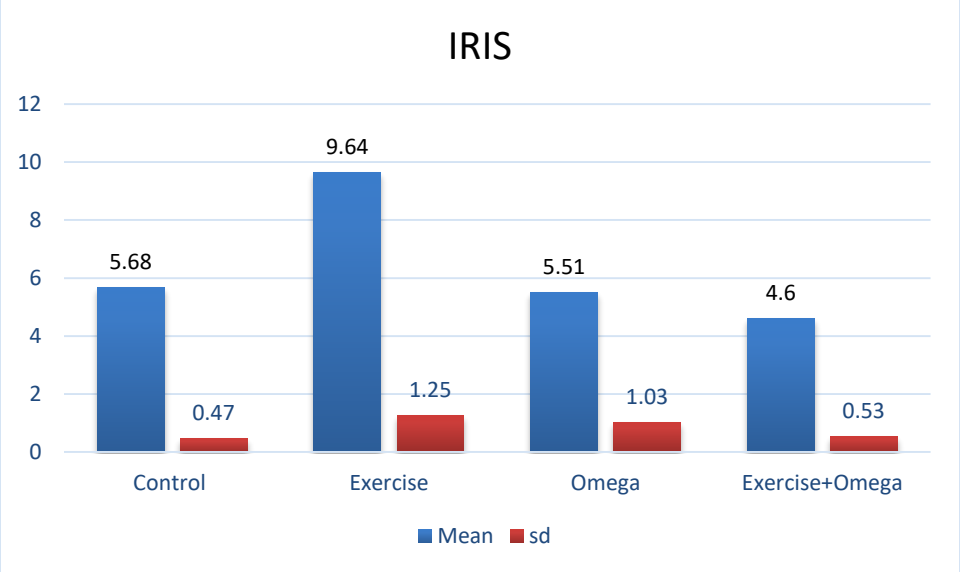

Figure 1. Comparison of Iris Levels Between Groups

Considering the irisin levels in Figure 1, it was seen that the exercise group had a significant increase in irisin values compared to the control group (p<0.05). Although there was a decrease in irisin hormone level in omega group compared to the control group, no statistically significant difference was observed (p > 0.05). The biggest change in irisin levels occurred in the exercise group, and it was determined that exercise caused a difference in irisin levels as the source of this. In addition, a statistically significant decrease was found in irisin values in the exercise + omega supplement group compared to the control group (p<0.05).

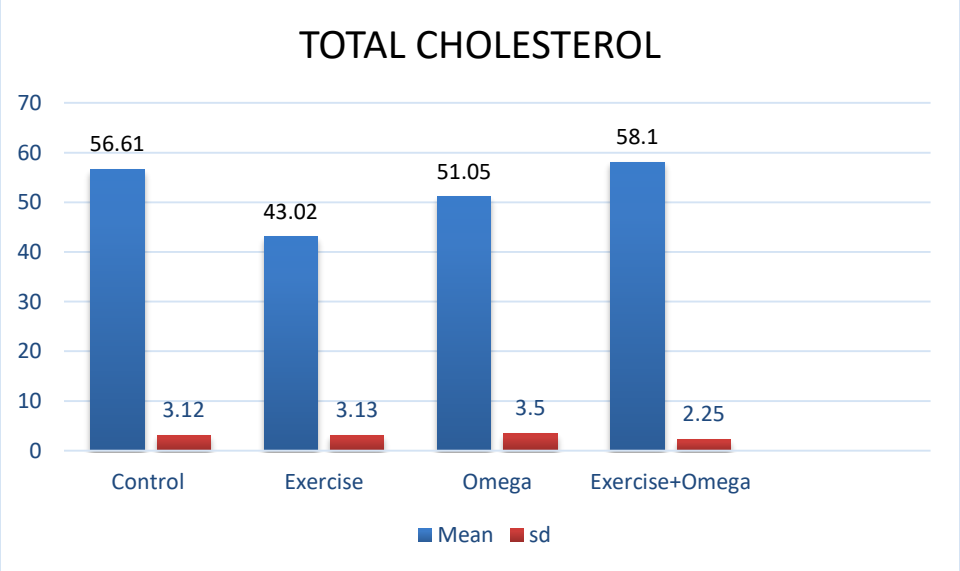

Figure 2. Comparison of Total Cholesterol Levels Between Groups

Average total cholesterol levels were examined in Table 1 and Figure 2, and it was observed that there was a statistically significant decrease in cholesterol levels in the exercise group compared to the control group (p<0.05). While the lowest total

cholesterol level was 43.02 mg/dL in the exercise group, the highest cholesterol level was 58.10 mg/dL in the exercise + omega group. There was no difference in total cholesterol levels between the control group and the exercise+omega groups ($p<0.05$). When the cholesterol levels between the omega group and the control group were examined, a significant decrease was detected ($p<0.05$).

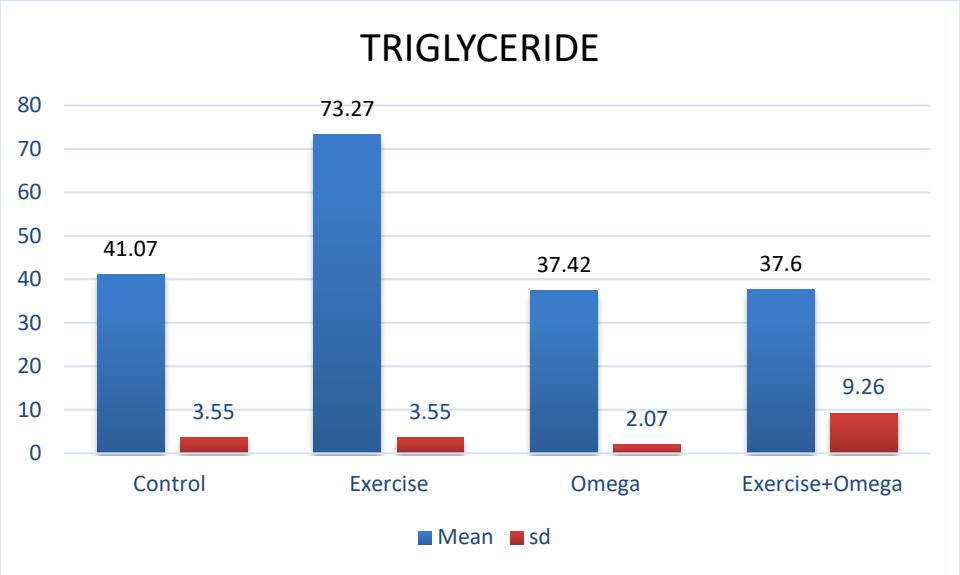

Figure 3. Comparison of Triglyceride Levels Between Groups

Average serum triglyceride concentrations are shown in Figure 3 and Table 1. Considering the triglyceride levels in the figure, it was determined that there was a significant increase in the exercise group compared to the control group ($p<0.05$). It was observed that the triglyceride concentration levels of the omega group decreased significantly compared to the control group ($p<0.05$). There was no significant difference between triglyceride concentration levels between omega and exercise+omega groups ($p<0.05$).

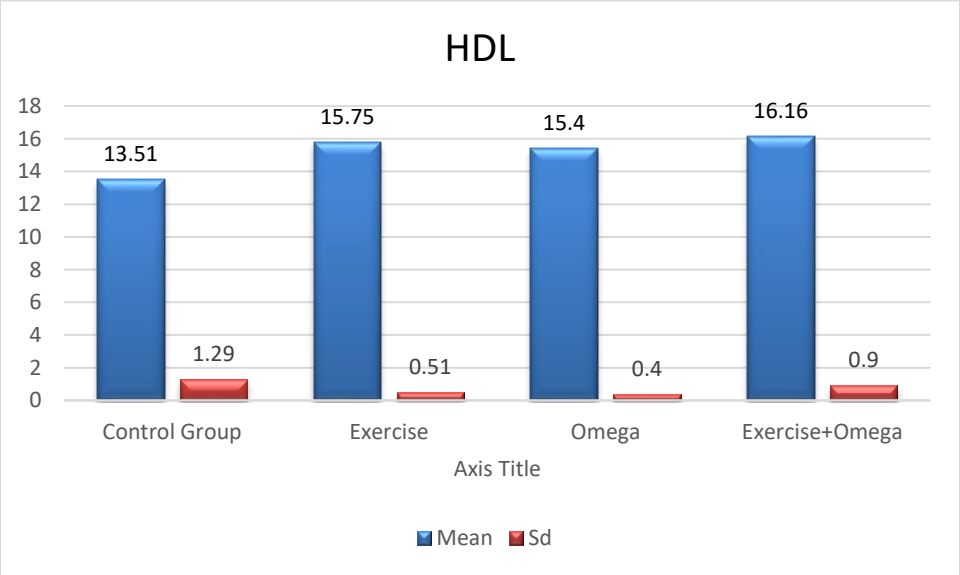

Figure 4. Comparison of HDL Cholesterol Between Groups

HDL cholesterol levels are shown in Figure 4 and Table 1. When the HDL cholesterol levels in Figure 4 were examined, a significant increase was observed in the cholesterol levels of the exercise, omega and Exercise+Omega groups compared to the control group ($p<0.05$ There was no difference between the exercise group and omega groups in terms of HDL cholesterol concentration levels ($p<0.05$). However, when we examined the HDL cholesterol levels in the Exercise+Omega group versus the exercise and omega group, it was seen that there was a numerical increase in the Exercise+Omega group, although not statistically.

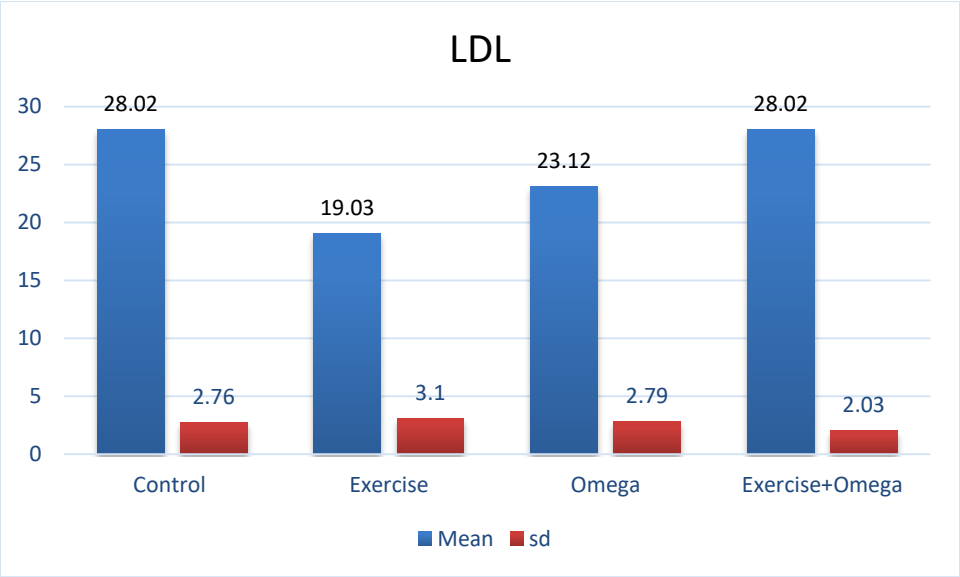

Figure 5. Comparison of LDL Cholesterol Between Groups

LDL cholesterol levels are shown in Figure 5 and Table 1. When we examined the LDL cholesterol concentrations in Figure 5, it was determined that there was no statistically significant difference between the control group and the exercise + omega group. A statistically significant decrease was found in LDL cholesterol levels in the exercise group versus the control group ($p<0.05$). In addition, a significant difference was found between the exercise and omega groups ($p<0.05$).

4. DISCUSSION

In this study, we investigated the effects of omega-3 fatty acids and exercise on irisin hormone, total cholesterol, HDL, LDL and triglyceride levels when applied separately and in combination. A group of researchers investigating the effect of aerobic exercises on circulating irisin concentration levels reported that aerobic exercises performed three days a week for twelve weeks produced an increase in irisin levels. (Jedrychowski et al., 2015). In a study investigating the effects of moderate-intensity aerobic exercise on irisin hormone in young men and women, it was determined that exercise caused a significant increase in irisin levels (Kraemer et al., 2014). In a clinical study by Huh et al, it was determined reported that moderate-intensity aerobic exercises increase the level of irisin in the circulation, and the level of increase in irisin levels in healthy individuals and patients with metabolic syndrome is at the same rate. (Huh et al., 2014). Lee and So (2014) reported that 2-month endurance exercises increased circulating irisin levels. In another study, it was reported that swimming exercise for 16 weeks caused a statistically significant increase in the level of circulating irisin (Kim and Kim, 2018; Lee and So, 2014). In addition, there are different studies (Khalafi et al., 2016; Küçük, 2018; Kabasakalis et al., 2019) revealing that aerobic exercise causes an increase in irisin levels. When we examine the literature studies, it is seen that our study is similar to the literature; It can be stated that the irisin level in the exercise group was higher than the other groups, and the increase in the irisin level occurred as a result of the exercise increasing the FNDC5 secretion, which triggers the iris by initiating the PGC1 α secretion. However, when we examine the literature studies, there are studies reporting that exercise does not affect circulating irisin levels. In a study examining the effects of different types of exercise on irisin levels, it was reported that there was no relationship between exercise and irisin levels. They reported that in the absence of a relationship between exercise and irisin, there may be different factors affecting the transcription of genes that affect PGC-1α and FNDC5 secretion (Pekkala et al., 2013). In an in vivo and in vitro study, they reported that exercise did not affect circulating irisin levels. However, they reported that irisin levels are associated with muscle type, muscle strength and muscle endurance (Kurdiova et al., 2014). They reported that 12-week strength training in sedentary female individuals did not affect circulating irisin levels, but FNDC5 secretion was associated with muscle fiber types (Ellefsen et al., 2014). It can be stated that these different results in the studies on exercise and iris are due to the variables such as experimental models, type of exercise, exercise intensity, acute and chronic exercise.

It has been suggested that leptin improves glucose balance and suppresses lipid metabolism in adipocytes, but the mechanism of these effects has not yet been fully elucidated. According to Pancar et al. (2022) found that the highest leptin levels were in the energy supplement group, and the lowest levels were in the exercise group, and reported that there was no difference between the groups when the other groups were compared. Most studies on leptin (Zhao et al., 2011; Gomez-Merino et al., 2002) seem to have focused on obesity or acute exercise and plasma leptin levels. Overall, these studies show that exercise intensity and energy

expenditure significantly alter plasma leptin levels. As a result of the study, Temur and Item (2020) determined that 8 weeks of moderate exercise first decreased leptin levels and then increased them again; reported that there was no significant difference between pre-test, mid-test and post-test values ($p>0.05$). Pancar et al. (2022) reported that the lowest ghrelin levels were found in the supplement group, the highest levels were found in the supplement+exercise and exercise groups, and there was no statistically significant difference between the groups. group, they stated that the given energy drink aroused a feeling of satiety and decreased appetite stimulation. In our study, the highest ghrelin levels were found in the exercise group, and the lowest levels were found in the omega group. These results suggest that regular exercise of moderate intensity increases ghrelin levels.

It is stated that regular exercise increases mitochondrial protein synthesis and this causes a decrease in the lipid content of white adipose tissue. This exercise-induced improvement in mitochondrial functions ensures the regulation of adipokines and this metabolic process occurs in response to exercise (Stanford et al., 2015). In a study conducted on rats, the effects of different fatty acids on lipid metabolism were examined and it was determined that omega-3 fatty acids lowered total cholesterol and triglyceride levels and increased HDL cholesterol levels compared to other fatty acids (Mohamed et al., 2002). In a similar study, reported that fish oil supplementation reduced triglyceride and total cholesterol levels and improved HDL cholesterol levels (Aguilera et al., 2002). In another study, determined that zinc supplementation applied together with regular exercise had significant effects on fat and glucose metabolism (Erdogan et al., 2021). In a study examining the effects of different oil contents on lipid metabolism, it was observed that triglyceride, total cholesterol and HDL values were the lowest in the fish oil group (Chi et al., 1999). However, the decrease in HDL level contrasts with the results of our study. In another study, similar to the results we found, it was reported that omega-3 supplementation caused a significant decrease in triglyceride levels (Clandinin et al., 1997).

The regulation of lipid metabolism may vary according to the n-3 PUFA type as well as fat storage. For example, EPA is preferentially directed towards β-oxidation, while DHA and DPA are protected from catabolism and accumulated in tissues (Ghasemifard et al., 2015). In addition, gene expression of hormone-sensitive lipase, lipoprotein lipase and phosphoenolpyruvate carboxykinase used for fatty acid synthesis in adipose tissue in the retroperitoneal region is decreased with DHA and mixed EPA/DHA supplementation, but not with EPA supplementation alone (Lucero et al., 2017; Raclot et al. et al., 1997). Omega-3 PUFAs reduce lipogenesis and cause decreased hepatic VLDL secretion (Sato et al., 2010). Wu et al. In an in-vitro study conducted by MD, it was observed that omega-3 fatty acid supplementation decreased VLDL secretion and apolipoprotein B100 production in the improvement of HepG2 cells (Wu et al., 1997). This effect of omega-3 fatty acids has been confirmed in a study on experimental animals (Chadli et al., 2012). Thus, omega-3 fatty acids can inhibit VLDL formation, limiting the supply of fatty acids to adipocytes, thereby limiting adipocyte size and mass. In addition, studies on experimental animals have shown that omega-3 supplementation increases circulating HDL cholesterol concentration by modulating changes through cholesterol ester transfer protein (Kasbi et al., 2013; Xie et al., 2016). Omega-3 fatty acids increase the expression of both element-binding protein-1 (SREBP-1), a transcription factor, and ChREBP, which is involved in fatty acid synthesis and cholesterol regulation (Chadli et al., 2012; Kim et al., 1999). Nuclear translocation of ChREBP is inhibited by n-3 PUFAs, resulting in decreased expression of lipogenic and glycolytic genes, including FAS and pyruvate kinase, respectively (Dentin et al., 2005). Furthermore, n-3 PUFAs suppress hepatic lipogenesis by reducing both messenger RNA (mRNA) and active protein expression of SREBP-1c, which in turn inhibits many genes involved in lipogenesis, including carboxylase of FAS and acetyl-coenzyme a. causes a decrease in its expression (Sekiya et al., 2003; Kaur et al., 2011). PPAR-γ, which is the main regulator of adipogenesis, is involved in the control mechanism of several genes and adipokines in lipid and glucose metabolism. Omega-3 fatty acids act as ligands for PPAR-γ (Neschen et al., 2006). Omega-3 fatty acids increase the binding of PPAR-y to the PPAR response element in the promoter region of vascular endothelial growth factor-A, which supports adipogenesis and alleviates hypoxia-induced adipocyte inflammation and insulin resistance (Hasan et al., 2015). Mitochondrial biogenesis and fatty acid metabolism PPAR-a and Cox3 in rodent liver (Willumsen et al., 1993), adipose tissue (Flachs et al., 2005), and small intestine (Van-schohorst., 2009), possibly through stimulation of omega-3 fatty acids. reported to increase oxidation. Activation of PPAR-α can also increase fatty acid oxidation. Increases in fatty acid oxidation by n-3 PUFA are mediated by AMPK, a known regulator of cellular energy metabolism (Figueras et al., 2011).

In our study, the effects of exercise and omega-3 fatty acids on HDL, LDL, total cholesterol and triglyceride concentrations, both separately and in combination, were determined in rats. In this study, it was determined that the total cholesterol level decreased in the exercise and omega applied groups compared to the control group. However, it was observed that the combined use of exercise and omega-3 supplements caused an increase in total cholesterol levels. When we examined the triglyceride levels, it was determined that there was a significant increase in the exercise group compared to the control group. When we examined the omega-3 and exercise group, it was observed that there was a decrease in triglyceride concentration. When we looked at HDL levels, it was determined that there was an increase in all three groups compared to the control group. Finally, when we examined LDL levels, it was determined that it decreased in the exercise and omega group, but combined exercise and omega-3

supplementation did not cause a change in LDL levels. In line with these results, n-3 PUFAs regulate lipid metabolism, promote fatty acid oxidation and suppression of lipogenesis, and lead to a favorable lipid profile and adipocyte metabolism. However, studies determining the effects of omega-3 fatty acids on lipid metabolism differ. It can be thought that this situation is caused by genetic differences between living species, blood and tissue parameters of humans and animals being affected differently by nutritional factors, and the fact that endogenous lipid metabolism varies according to factors such as hormonal, genetics and age.

According to the results obtained in our research; As in the literature, on the lipid profile, which is considered as risk markers for coronary heart diseases and that regular exercise causes an increase in irisin levels; It has been determined that there are increases in HDL cholesterol levels, which are called benign, while decreases in LDL cholesterol levels, which are also called malignant. In addition, similar to the results of literature studies, it has been determined that exercise has a healing effect on total cholesterol level. According to the results of the findings; Similar to the results obtained in the literature studies, it was determined that there was an increase in HDL levels and a decrease in total cholesterol and LDL levels in the omega-3 supplement group. As a result, it can be stated that both exercise and omega-3 fatty acid supplementation have positive effects on the lipid profile and our study is in line with the literature.

It is known that with the increase in irisin levels, there is an increase in fat burning and energy consumption. For this purpose, we aimed to clarify whether omega-3 supplementation and exercise, when applied separately or in combination, mediate changes in irisin hormone levels, which are also effective in fat burning. As a result of the analysis of the data we obtained; It was determined that irisin levels decreased in the omega-3 supplementation group compared to the control group, although it was not statistically significant. When exercise and omega-3 supplementation were applied in combination, it was determined that irisin levels decreased statistically significantly compared to the control group. In a study examining the effects of omega-3 fatty acids on skeletal muscle cells, inconsistent with the results we obtained, it was found that omega-3 fatty acid supplementation caused an increase in PGC-1α and GLUT-4 levels, which trigger irisin induction and increase its secretion, and as a result of this increase, irisin levels increased. It has been found to occur (Vaughan et al., 2012). When we examine the studies in the literature investigating the effects of omega-3 supplementation on irisin hormone and lipid profiles, the effects of omega-3 supplementation on irisin hormone and lipid profile vary. It can be stated that the source of these variable results is genetic differences between living species, blood and tissue parameters of humans and animals are affected differently by nutritional contents, experimental model differences, health status of the subjects participating in the study and differences in supplement dosage. The number of studies on the effects of omega-3 fatty acids on the iris and the mechanisms that mediate these effects is almost negligible. In this context, we can say that our study will make a great contribution to the literature.

5. CONCLUSION

As a result; It was determined that omega-3 fatty acid supplementation did not cause any change in irisin levels. It is known that exercise causes an increase in irisin hormone levels, but in our study, it was determined that irisin hormone caused a serious decrease in the Exercise + Omega-3 group compared to the control and exercise groups. According to this result we have determined, it is not known why omega-3 fatty acid supplementation applied together with exercise reduces the irisin level or how this mechanism is affected, and this issue needs to be clarified.

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Ethical approval

This study was approved by Van Yüzüncü Yıl University Animal Experiments Local Ethics Committee (Protocol No: 2021/02-12 Date: 25/02/2021).

Author's note:

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Conflicts of interest

The authors declare that there are no conflicts of interests.

Data and materials availability

All data associated with this study are present in the paper.

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