EURASIAN JOURNAL OF HEALTH SCIENCES
e-ISSN 2651-3501

Eurasian JHS 2023; 6 (3): 26-33

Research Article/
Araştırma Makalesi

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# The Effect of Moderate Exercise on Liver Function, Lipid Peroxidation and the Lipid Profile in Rats Fed a High-Fat or Standard Diet

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## ABSTRACT

Objective: It is a well-known fact that a diet which contains excessive fat and the factor ofobesity are the triggers and the culprits of many diseases. Furthermore, it is also known that exercise increases the level of physical fitness, affects general health positively and plays an active role in preventing various diseases. This study investigated the effect of moderate exercise on liver function, lipid peroxidation and the lipid profile in rats which were fed with a high fat or a standard diet. Method:Twenty-four Wistar albino rats were randomly divided into four groups, namely; control, exercise, high-fat diet (HFD) and HFD+exercise (n=6 for each group). After 8 weeks of study;glucose, lipid profile, liver function tests, gamma-glutamyltransferase (GGT) activities and the malondialdehyde (MDA)levels were measured in both serum and liver.Results: Glucose levels in the HFD+E group were lower than the control and exercise groups ($p<0.05$).The serum MDA level in the HFD+E group was lower than in the HFD group ($p<0.05$). AST and ALT activities and the MDA level in liver lysates were lower in the HFD+E group than in the HFD group ($p<0.05$). In addition,serum LDH and GGT activities were increased in the exercise group when compared with the control group ($p<0.05$). Conclusion:This data showed that moderate exercise has a regulatory effect on lipid profile, lipid peroxidation and liver enzymes.

**Key words:** Exercise, High Fat Diet, Lipid Profile, Lipid Peroxidation, Liver Function Tests.

# Yüksek Oranda Doymuş Yağlı veya Standart Diyet ile Beslenen Sıçanlarda Orta Düzey Egzersiz'in Karaciğer Fonksiyonu ile Lipit Peroksidasyonu ve Lipit Profili Üzerine Etkisi

## ÖZ

Amaç: Aşırı yağlı diyetle beslenme ve obezitenin birçok hastalığın tetikleyicisi ve sorumlusu olduğu çok iyi bilinen bir gerçektir Egzersizin fiziksel uygunluğu artırdığı, genel sağlık durumunu olumlu yönde etkilediği ve hastalıklardan korunmada etkin rol oynadığı bilinmektedir. Bu çalışmada yüksek yağlı veya standart diyetle beslenen sıçanlarda orta derecede egzersizin karaciğer fonksiyonu, lipit peroksidasyonu ve lipit profili üzerindeki etkisi araştırıldı.Yöntem: 24 adet Wistar albino sıçanı rastgele kontrol, egzersiz, yüksek yağlı diyet (HFD) ve HFD + egzersiz (n = 6) olarak dört gruba ayrıldı.8 hafta süren çalışma sonunda hem serumda hem de karaciğerde glikoz, lipit profili, karaciğer fonksiyon testleri, gamma-glutamiltransferaz (GGT) aktiviteleri ve malondialdehit (MDA) düzeyi ölçüldü. Bulgular: HFD+E grubunda glikoz seviyeleri kontrol ve egzersiz grubuna göre düşük olduğu saptandı ($p<0.05$). HFD+E'de serum MDA seviyesinin HFD' grubuna göre düşük olduğu görüldü ($p<0.05$). Karaciğer lizatlarında AST ve ALT aktiviteleri ve MDA seviyesi HFD+ E'de HFD'ye göre daha düşüktü ($p<0.05$). Ayrıca egzersiz grubunda serum LDH ve GGT aktivitelerinin kontrol grubuna göre arttığı bulundu ($p<0.05$). Sonuç:Bu veriler, orta derecede egzersizin lipit profili, lipit peroksidasyonu ve karaciğer enzimleri üzerinde düzenleyici bir etkiye sahip olduğunu gösterdi.

**Anahtar Kelimeler:** Egzersiz, Karaciğer Fonksiyon Testleri, Lipit Profili, Lipit Peroksidasyonu, YüksekYağlı Diyet.

DOI: 10.53493/avrasyasbd.1224512 Received: 26.12.2022 Accepted: 11.05.2023

## INTRODUCTION

It has long been known that maintaining a HFD is an important risk factor for health problems such as obesity, diabetes and metabolic syndromewhich leads to Alzheimer's disease and various cognitive disorders. Saturated fats are classified as fats that are responsible for heart disease since they induce an increased circulation oflow-density lipoprotein (LDL) and raise cholesterol levels (Di Nicolantonio et al. 2018). Hightotal and LDL cholesterol levels in childhood are associated with an increased risk of cardiovascular diseases in advanced ages (Srinivasan et al. 2006). Therefore, the lipid profile presented with dietary fats is used in the assessment of the risk of heart disease (Weintraub et al. 1988).All the more,it has been reported that nourishment provided with high levels of dietary fat may cause a fatty liver and deterioration in liver function tests (Kouba-Ghorbel et al. 2020).

Anincrease in liver function tests is generally caused by non-alcoholic fatty liver disease (NAFLD), hemochromatosis, hepatitis B, hepatitis C, illegal drugs, diet products and psychiatric drugs (Friedman 2015). Regular and frequent moderate exercise supports the immune system and prevents the occurrence of several common diseases, including type 2 diabetes, obesity and cardiovascular diseases, while at the same time improving the mental health of the individual and preventing depression (Stampfer et al. 2000).This study investigated whether moderate exercise hadan effect on liver function, lipid peroxidation and the lipid profile in rats which were fed with a HFD or a standard diet.

## MATERIALS AND METHOD

### Experiments and Diet Application

This study was performed on 24 male Wistar albino rats, which were randomly divided into four groups (n=6 per group). Excluding the experimental diet, all other conditions were provided within the context of the laboratory and according to animal care standards.Thegroups were created as follows; the control group: a standard diet was provided (2.8% crude fat, 23.1% crude protein, 5% crude fibre, 7.1% crude ash and 12.8% moisture).The exercise group: a standard diet was provided and rats were subjected to a standard exercise routine for 3 days a week. The HFD group: 300g/kg(margarine /pellet meal) margarine was melted into a standard pellet meal(so 60% of energy consumed came from saturated fat);and was prepared and provided daily (Günbatar and Bayıroğlu 2015). Finally, the HFD+E group:in addition to a HFD, the rats in this group underwent a standard exercise routine for 3 times a week. The study lasted for8 weeks (Kartinah et al 2018).

At the end of the study, glucose, triglyceride, total cholesterol, HDL and LDL levels were measured in serum samples.The level of malondialdehyde (MDA)and the activities oflactate dehydrogenase (LDH), gamma-glutamyltransferase (GGT), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were measured in serum samples and liver lysates.

### Serum Separation from Blood Collectedin Biochemistry Tubes

Intra-cardiac blood collected at the end of the study was placed in yellow-capped biochemistry tubes and centrifuged at 3500 xg for 10 minutes. The supernatant serum was transferred to another tube and kept at -80°C until it was studied.

### Lysate Recovery from Liver Tissue Samples

To 200 mg livertissue,1.8mL of 20 mM Tris-HCl buffer (pH 7.4) was added (1/10, w/v), and the mixture was homogenised with the aid of a homogenizer (Ultra Turrax-T25). Next, the lysate was centrifuged at 10000g at 4°C for 30 minutes. The supernatant was transferred to a new Eppendorf tube. All samples were stored at -80°C until the process of biochemical measurements (Turkan et al. 2018a, 2018b).

### Measurement of Routine Biochemistry Parameters

Glucose, triglyceride, total cholesterol, HDL and LDL levelsas well as LDH, GGT, AST and ALT activities were measured by a chemical-luminescent micro-particle immunological method in a biochemistry analyzer (Abbott Architect I4000 SR, from USD) using kits and calibrators compatible with the device. The enzyme activities are expressed as U/L, and all other parameters are expressed as mg/dL.

### Measurement of MDA

MDA was measured according to the method of Khoschsoret al. (2000).Fifty micro-liters of serum or liver lysate were placed in a tube; 750 µL of phosphoric acid solution (0.44 M), 250 µL of thiobarbituric acid (TBA) solution (42 mM) and 450 µL of distilled water were addedto thesamples. The tubes were tightly closed and kept in a boiling water bath for 60 minutes. Then, they were cooled on ice and/or in tap water. Alkaline methanol (a mixtureof 50 mL pure methanol and 4.5 mL of 1 M NaOH) was added at a ratio of 1:1 (i.e. 1.5 mL, total volume 3 mL), and the mixture was centrifuged at 2,500 gfor 3 minutes. Two hundred micro-liters of the supernatant remaining in the upper part was transferred to a vial and loaded into a high-pressure liquid chromatography(HPLC) device. For the standard curve, 50, 25, 12.5, 6.25 and 3.125 mM solutions were prepared from 200 mM 1,1,3,3-tetraethoxypropane stock solution. For standard solutions, the procedure applied to the samples was as follows; aRP18 column,150 × 4.6 mm and 5µm particle width, For the mobile phase, 400 mL of 50 mM phosphate buffer (pH 6.8) and 600 mL of absolute methanol were mixed. The flow rate of the device was set to 0.8 mL/min. and the injection volume was 20 µL. Standards and samples were read at 527 nmemission and 612 nm excitation in fluorescence detectors (Khoschsorur et al. 2000).

### Exercise Program

The exercise programemployed a rat-specific treadmill. To ensure the adaptation of the rats in the exercise group to the treadmill, they were placed on the apparatus at the lowest speed level of the protocol (15 min/day and a speed of 10 m/min)for 2 weeks. During the 8-week study period, the rats received moderate exercise 3 days per week for 30 min/day at a speed of 24 m/min. This exercise program was applied according to a protocol developed by Rico et al (1999).

### Statistical Analysis

Descriptive statistics of the groups are presented in the forms of mean and standard deviation. The Shapiro–Wilk test was used to check whether the data was normally distributed. For each parameter, the Kruskal–Wallis test was used to evaluate whether the differences between groups were significant. Post hoc analysis (Tukey's honest significance test) was performed in order to determine the differences between groups. A pvalue ≤ 0.05 was considered significant.

## RESULTS

The serum glucose level in the control group was found to be higher than the other groups ($p<0.05$). However, the glucose level in the HFD+E group was lower than the control and exercise groups ($p<0.05$). In addition, the serum triglyceride level was higher in the HFD group when compared with the other groups ($p<0.05$), while the total cholesterol and LDL levels in the HFD group were only higher than the control and exercise groups ($p<0.05$).The serum triglyceride, total cholesterol and LDL levels in the exercise group were lower than the control group, but thedifferences were not significant ($p> 0.05$). In addition, the serum triglyceride, total cholesterol and LDL levels in the HFD+E group were lower thanin the HFD group, butthe differences were not found to be significant ($p> 0.05$). The situation was slightly different in terms of HDL,the good cholesterol indicator. In the exercise group, the HDL level was numerically higher than in the control group, but not significantly different ($p> 0.05$).In the HFD group, the HDL level was significantly lower compared with the control and exercise groups ($p<0.05$). The HDL level in the HFD+E group was slightly lower than the HFD group, but the difference was not significant ($p> 0.05$) (Table 1).

The serum ALT activity was higherin the HFD group compared with the other groups ($p<0.05$); however, this increase was only significant compared with the exercise group ($p<0.05$). In addition, although the serum ALT activity in the HFD+E group was lower thanin the HFD group, this difference was not significant ($p>0.05$). Theserum AST activity in the exercise group was slightly higher thanin the control group, but the differencewas not significant ($p>0.05$). However, the serum AST activity in the HFD group was significantly higher than inthe other groups ($p<0.05$). There was no difference in the serum AST activities of the other groups ($p> 0.05$) (Table 1).

Among the liver function indicators,the serum LDH and GGT activities in the exercise group were higher than the control group, but lower in the HFD and HFD+E groups compared with the control group (p<0.05). The lowest serum LDH activity was in the HFD group (p<0.05). In addition, the serum LDH activity of the HFD+E group was higher thanthe HFD group (p<0.05) (Table 1).

The serum level of MDA, the indicator of lipid peroxidation, was lower in the exercise group compared with the control group (p<0.05). The serum MDA level of the HFD group was significantly higher thanthe other groups (p<0.05). However, the serum MDA level in the HFD+E groups was significantly lower compared with the HFD group (p<0.05).

**Table 1.** Mean and Standard deviation values of lipid profile and liver function tests regarding the serum samples.

| | Control | Exercise | HFD | HFD+Exercise | P Value |
|---|---|---|---|---|---|
| **Glucose (mg/dL)** | 312.00±19.05* | 229.25±21.72 | 212.00±7.16 | 190.80±18.30≠ | 0.001 |
| **Triglyceride (mg/dL)** | 72.82±4.96 | 67.96±4.51 | 98.33±9.81* | 84.40±8.80≠ | 0.001 |
| **Total Cholesterol (mg/dL)** | 54.00±3.52 | 50.43±3.14 | 69.83±3.97≠,¤ | 65.33±6.06≠,¤ | 0.001 |
| **HDL (mg/dL)** | 40.20±1.33 | 43.40±2.48 | 33.10±2.07≠,¤ | 35.10±3.68≠,¤ | 0.001 |
| **LDL (mg/dL)** | 7.58±0.51 | 6.72±0.72 | 13.52±1.79≠,¤ | 12.03±1.38≠,¤ | 0.001 |
| **ALT (U/L)** | 30.80±3.54 | 31.60±3.38 | 36.00±1.10≠ | 33.40±3.83 | 0.072 |
| **AST (U/L)** | 90.68±6.68 | 94.60±7.55 | 120.07±3.96* | 95.40±5.20 | 0.003 |
| **LDH (U/L)** | 1227.06±124.42* | 1382.04±91.62* | 519.12±30.41 | 603.40±48.80ø | 0.001 |
| **GGT (U/L)** | 1.76±0.08* | 1.97±0.16* | 1.43±0.05 | 1.36±0.15 | 0.001 |
| **MDA (nmol/mL)** | 1.58±0.12 | 1.30±0.06* | 3.17±0.26* | 1.78±0.11≠,ø | 0.001 |

*p: It is significant compared to other groups (p<0.05), ≠p: It is significant compared to the exercise group (p<0.05),¤p: It is significant compared to the control group (p<0.05), øp: It is significant comparedto the HFD group (p<0.05). HDL: high-densitylipoprotein, LDL: low-densitylipoprotein, AST: aspartatetransaminase, ALT: alaninetransaminase, LDH: lactatedehydrogenase, GGT: gamma-glutamyltransferase, MDA: malondialdehyde.

The changes in AST, ALT and LDH activities in liver lysates were more pronounced than those measured in the serum samples. While the liver ALT, AST and LDH activities in the exercise group were higher than the control group, only the ALT activity was significantly different (p < 0.05). In addition, the liver ALT, AST and LDH activities in the HFD group were found to be significantly higher than the other groups (p<0.05). The liver AST and ALT activities were significantly lower in the HFD+E when compared with the HFD group (p<0.05) (Table 2).

The liver GGT activity showed a different pattern. Although the liver GGT activityinthe exercise group was higher than the control group (p<0.05), there was no difference in this activity between the HFD and control groups (p>0.05). In addition, the liver GGT activity in the HFD+E group was higher when compared with the HFD group (p<0.05). The MDA level in the HFD group washigh when compared with the other groups (p<0.05). The MDA level in the HFD+E group was lower than the HFD group (p<0.05). Other detailed results are shown in Table 2.

**Table 2.** Mean and standard deviation values of liver function tests and lipid peroxidation in liver lysates.

| | Control | Exercise | HFD | HFD+Exercise | P Value |
|---|---|---|---|---|---|
| **ALT (U/mg protein)** | 0.56±0.05* | 1.89±0.21* | 3.68±0.10* | 2.43±0.37* | 0.001 |
| **AST (U/mg protein)** | 1.10±0.03 | 1.28±0.18 | 9.92±0.62* | 1.89±0.08* | 0.001 |
| **LDH (U/mg protein)** | 3.58±0.25 | 3.88±0.21 | 5.26±0.32* | 4.11±0.28≠,¤ | 0.001 |
| **GGT (U/mg protein)** | 0.46±005 | 0.69±0.03* | 0.51±0.04 | 0.59±0.03* | 0.001 |
| **MDA (µmol/mg protein)** | 0.24±0.02 | 0.21±0.02 | 0.48±0.06* | 0.29±0.03≠,ø | 0.001 |

*p: It is significant compared to other groups (p<0.05). ≠p: It is significant compared to the exercise group (p<0.05),¤p: It is significant compared to the control group (p<0.05), øp:It is significant compared to the HFD group (p<0.05). AST: aspartate transaminase, ALT: alanine transaminase, LDH: lactate dehydrogenase, GGT: gamma-glutamyltransferase, MDA: malondialdehyde.

## DISCUSSION

It has been reported that common risk factors for dyslipidaemia include high cholesterol, a high triglyceride level, increased LDL and decreased HDL (Esteghamti et al.2006). Elsayyad et al. (2020) reported that serum LDL, total cholesterol and triglyceride levels were lower in the control group after the application ofan 8-week regular aerobic exercise program, but the HDL level was significantly higher in the control group. Kazeminasab et al. (2013) reported that a regular 20–30 minutes of exercise a day, for five times a week and for 8 consecutive weeks decreased LDL and TG levels and increased the HDL level when compared with the control group.

In the present study, although serum triglyceride, total cholesterol and LDL levels were found to be lower in the exercise group when compared with the control group, the differences were not significant. In addition, the HDL level in the exercise group was higher than the control group, but the difference, again was not significant. Althought here were numerically lower serum triglyceride, total cholesterol and LDL levels and a higher HDL level in the HFD+E group compared with the HFD group, the differences between the groups were not significant (Table 1).While the mechanism of the effects of aerobic exercise on lipids and exercise-induced lipid changes is unclear, regular exercise reportedly increased lipid consumption and decreased lipid levels with increasing lipoprotein lipase (LPL) activity (Earnest et al. 2013).In the current study,these changes in the lipid profile may be caused by an increased LPL activity.

Embay et al. (2016) reported that the blood glucose level decreased significantly after aerobic exercise when compared with the control group.Furthermore, in another study, Iscoe and Riddell (2011) reported that the blood glucose level decreased after aerobic exercise as well. In this study, the serum glucose level was higher in the control group when compared with the other groups. However, the glucose level in the HFD+E group was lower than the control and exercise groups (Table 1).The low glucose level observed in this study may have resulted from the effect of moderate exercise which increases glucose utilizationin the muscles.

LDH is normally a cytosolic protein, but it serves as a cell damage indicator in the serum. Exercise causes a significant increase in the LDH activity (Gombacci et al.2002). Reichel et al.(2020) reported that LDH activity increased 24 hours after physical exercise.In our study, serum LDH was significantly increased in the E group when compared with the control group. In addition, the serum LDH activity of the HFD+E group was higher than the HFD group (Table 1). The liver LDH activity increased in the HFD+E group when compared with the control group (Table 2). It has been reported that increased LDH after exercise is due to increased damage in muscle cells (Ayca et al. 2012). In the present study, the tissue samples which were taken immediately after exercise showed anexercise-induced muscle damage and an increased lactate accumulation. Thus, this may be the reason of the increased LDH levels in the exercise groups.

GGT is produced in the liver (Emdin et al.2005), and its serum level is accepted as an indicator of general liver health.Shavandi

et al. (2012) found that the mean GGT value increased from 57.40 ± 31.51 before exercise to 137.60 ± 49.01 after exercise. Sadowska-Krępaet al. (2020) reported that the GGT value increased after the exercise.In our study,the serum GGT activitywas significantly increased in the exercise group when compared with the control group. The lower serum GGT activity in the HFD+E group not found to be significant when compared with the HFD group (Table 1). Regarding liver lysates, the GGT activity increased in the exercise and HFD+E group when compared with the control and HFD groups (Table 2). An increased GGT concentration is associated with liver insulin resistance, insulin secretion and liver insulin loss andthese changes can vary depending on individual physiological differences. There is a positive correlation between a high GGT level and a high body mass index, diabetes and high blood pressure (Armand and Darvakh 2015). In the current study,the increased GGT activityin the exercise groups can be explained byphysiological differences and by the high glucose levels which were observed in the rats included in the study (Table 1).

MDA is an important marker which reflects low-grade systemic inflammation (Bulloet al.2003). Witayavanitkul et al. (2020) reporteda non-significant decrease in the liver MDA level after a 5-week moderate exercise protocol. It was reported that MDA values decrease after awalking exercise (Johnson et al.2012). In another study, Lima et al. (2018) reported a decrease in the MDA level after exercise. In our study, the serum MDA levelswere consistent with most of the abovementioned studies and were found to be significantly lower in the exercise and HFD+E groups when compared with the control and HFD groups, respectively (Table 1). The same result was seen between the HFD+E and HFD groups in liver lysates (Table 2). While the MDA level increased immediately after exercise, itdecreased after 24–48 hourspost-exercise. Depending on the intensity of the exercise, oxidative reactions and antioxidant capacity may be impaired, and the MDA level may increase as a result of subsequent lipid peroxidation (Marzatico et al.1997). In the present study, the low MDA level observed in the exercise groups may be due to the fact that the moderate exercise programlowered several components of the lipid profile. These changesmay have regulated oxidative reactions and the antioxidant capacity.

AST is not a specific indicator of liver damage contrary to ALT because of its multiple organ distribution. ALT is used as an indicator of liver damage because of its extensive expression of the organ.Itis also found in small amounts in the kidneys, heart, muscles and pancreas (Leibowitz et al. 2012). Armand and Darvakh (2015) reported that ALT and AST values decreased after aerobic exercise. Shanb et al. (2009) reported a significant decrease in ALT and AST values after a treadmill exercise. In the present study, although serum ALT activity in the HFD+E group was lower than the HFD group, the differencewas not significant. Although serum AST activity of the Egroup was slightly higher than the control group, the differencewas not significant (Table 1). In liver lysates, AST and ALT activities were significantly decreased in the HFD+E group when compared with the HFD group (Table 2). These changes in the exercise groups, especially when compared with the HFD group, may have occurred due to moderate exercise causing a decrease in lipid transmission to the liver and increased hepatic oxidation.

## CONCLUSION

We conclude that moderate exercise does not cause cellular damage and it regulates the lipid profile and liver enzyme activities.We recommendthe conduction of longer-term moderate exercise studies.

## ACKNOWLEDGEMENTS

This study was supported by the Van YuzuncuYıl University Scientific Research Projects Coordination Unit (Project Number:2015 –VSYO-B256).

## AUTHOR CONTRIBUTION

Idea/Concept:NG, ZH; Design: NG, BB; Consultancy: NG; Data Collection and/or Processing: NG, ZH; Analysis and/ or Interpretation: NG, SE; Literature Review: NG, GO; Writing the Article: NG, ZH; Critical Review:NG

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## ETHICAL STATEMENT

The study was approved by the Van Yuzuncu Yıl University Animal Experiments Local Ethics Committee (date of decreeand number:03.10.2019/09).

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