Journal of Research in Applied and Basic Medical Sciences 2023; 9(4): 263-271

Original Article

RABMS Journal of Research in Applied and Basic Medical Sciences

# Investigating the effect of eight weeks of moderate-intensity aerobic exercise and taking curcumin supplement alone and in combination, on leptin levels and hepatic enzymes in older rats

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## Abstract

***Background & Aims*:** Non-alcoholic fatty liver disease is a common health problem in the world, and various studies have shown that the risk of developing the disease increases with age. In this study, we looked at the effects of 8 weeks of moderate-intensity aerobic exercise and curcumin use alone and in combination with each other on leptin and hepatic enzymes levels.

***Materials & Methods:*** 32 male Wistar rats (24-month-old), and 8 male rats with the same breed (4-month-old) were examined in 5 groups (8 rats per group). Two groups were young and old control groups, and three groups included exercise group, curcumin group, and curcumin + exercise group. SPSS18 software and one-way ANOVA method and Tukey's post hoc test were utilized and 0.05> α was considered statistically significant.

***Results:*** 8 weeks of aerobic exercise did not have a significant reduction in the level of leptin and hepatic enzymes, and 8 weeks of curcumin significantly reduced leptin levels and did not significantly reduce hepatic enzymes. Combined aerobic exercise and curcumin significantly reduced leptin and hepatic enzymes.

***Conclusion:*** Concomitant use of curcumin with moderate-intensity aerobic exercise can have positive effects on reducing leptin levels and hepatic enzymes in patients with non-alcoholic fatty liver disease.

***Keywords*:** Aerobic exercise, curcumin, non-alcoholic fatty liver, aging, leptin, hepatic enzyme

**Received 17 January 2023; accepted for publication 10 April 2023**

## Introduction

Aging is a complex physiological process caused by the progressive decline of multiple biological functions and homeostasis disorders (1). Aging affects all organs and systems of the body and gradually reduces the ability and function of organs. Like various organs, the liver also affects the aging process, and its functional and anatomical changes include a decrease in volume due to a decrease in blood flow and reproductive capacity, reduce the clearance of free radicals which leads to an increase in oxidative stress and its damage (2). Aging also impairs the lipid profile, which is

associated with an increased sebaceous septum in non-adipose tissue such as the liver (2). Non-alcoholic fatty liver disease (NAFLD) is a wide range of liver diseases characterized by the deposition of fat in the liver cells (Hepatocytes), which accounts for 5% of liver weight (2). On the other hand, although it was previously considered a simple fat deposition (Osteoarthritis), it is now well known that osteoarthritis can initiate progressive pathological changes in the liver, including severe inflammation, ballooning of liver cells, fibrosis changes and even Cirrhosis (2).

Steatosis, simple accumulation of fat (mainly triglycerides, phospholipids and cholesterol esters) in hepatocytes (3) is asymptomatic and reversible but occurs with age, liver damage, and inflammation (4). Steatosis mainly increases fat synthesis, a decrease in β-oxidation of fatty acids, an increase in the yield of fatty acids, and a decrease in the release of fatty acids from the liver in the form of VLDL (3). There are several laboratory methods for examining the disease, one of them is to study the circulating levels of the enzymes Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT), which are important blood indicators for liver health (5). The association of high levels of these hepatic enzymes with non-alcoholic fatty liver disease has been shown in various studies. Therefore, serum values of these enzymes can be evaluated to assess the situation of liver cells and patient diagnosis (6, 7). In non-alcoholic fatty liver, also the balance of adipokines is disturbed. Adipokines are important factors in liver disorders that cause damage to liver cells, inflammation, and eventually progressive fibrosis in the liver (8,9).

Inflammatory cells in adipose tissue cause Adipokines production and Adipokines play a key and functional role in the study of fatty liver damage during paracrine and endocrine mechanisms (10). The study results show that leptin levels increase in a non-alcoholic fatty liver (9) also, leptin loses its ability to reduce food intake and increase energy consumption (11). On the other hand, various studies have shown that lifestyle changes such as regular exercise and a suitable diet can control the progression of non-alcoholic fatty liver disease (12). An eight-week study of aerobic exercise found a significant reduction in the levels of the serum aspartate aminotransferase and alanine aminotransferase enzymes in patients with fatty liver (13). Kawanishi et al. (2012) also concluded in their study that 16 weeks of exercise on the rotating band has a reducing effect on hepatic enzymes in rats with non-alcoholic fatty liver (14).

Despite the results of the mentioned studies, other studies have shown that regular exercise has not altered the values of these indicators, indicating a discrepancy in the reports.

Also, in the study of Barzgarzadeh Zarandi et al. (2012), the levels of AST and ALT enzymes increased after 6 and 12 weeks of continuous and periodic exercise in older rats (15). Despite various studies in this field to date, there are no specific recommendations for exercise therapy in patients with NAFLD, such as type of exercise, intensity of exercise or duration of treatment that can provide the greatest benefit in reducing NAFLD. There is a severe lack of data to support the effect of exercise on the treatment of NAFLD (12). On the other hand, today the tendency to use drugs and herbal supplements and attention to the possible therapeutic effects and herbal supplements has increased because they may be considered as alternatives or supplements in the future beside medical interventions. Natural substances with various plant origin have been used in traditional medicine for the treatment and protection of the liver (16, 17). Curcumin is the main active ingredient in Turmeric, a yellow phenolic pigment which has a wide range of biological and pharmacological activities. In addition, curcumin is a powerful antioxidant and cleanser of free radicals that can prevent the production of a variety of free oxidant radicals in the biological environment (18).

Various studies have reported that curcumin supplementation can improve NAFLD. Studies show that curcumin has antimicrobial, anti-inflammatory, antioxidant, immune-boosting, anti-cancer, and liver protection properties which have been modified through signaling pathways and gene regulation (19). Since the effect of exercise and the consumption of curcumin each

alone or together on the metabolism of lipids and steatosis has received less attention due to aging, we believe that in this study, after examining the changes in hepatic enzymes and leptin, which are factors that involve in NAFLD due to aging, we evaluate the effects of eight weeks of moderate-intensity aerobic exercise and the use of curcumin alone and in combination with these parameters.

## Materials & Methods

In this study, 32 male Wistar breed rats, 24-month-old, (550-600 gr) and 8 male 4-month-old rats with the same breed (200-250 gr) were examined in five groups (8 rats per group).

1- ***Young control group***: In this group, animals were kept for 8 weeks.

2- ***Old control group***: In this group, old animals were kept for 8 weeks.

3- ***Exercise group***: In this group, old animals performed moderate-intensity aerobic exercise on a treadmill for 8 weeks and 5 days a week.

4. ***Curcumin group***: In this group, older animals were treated with curcumin for 8 weeks and 5 days a week. Curcumin was given to them by gavage.

5. ***Curcumin and Exercise Group***: In this group, older animals received curcumin for 8 weeks and 5 days a week, also they performed moderate-intensity aerobic exercise on treadmill.

The way animals are kept in the animal hold place is the same for all animals. The duration of this study is 8 weeks. It is noteworthy Dimethyl sulfoxide (DMSO) is the solvent for curcumin, and all animals that do not receive curcumin intervention are daily gavage with DMSO.

**How to do the exercise:**

***Introduction Protocol***: First, during the introductory phase, the animals were trained how to work on a rotating bar for two weeks by implementing a training protocol. The training program consisted of 5 running sessions on a rotating bar at a speed of 5 to 10 meters per minute with a zero slope for 10 minutes. For aerobic exercise, moderate-intensity by rat treadmills was used for rats. Mice were forced to run daily (5 days a week) at a speed of 18 m /min with a slope of zero degree for 2 months.

To minimize stress and do a moderate-intensity exercise, the exercise protocol was as follows: Animals in the exercise group exercised for 10 minutes at a speed of 5 m /min for the first week at a zero-degree slope, in the following weeks, 10 minutes were added to the exercise time and 5 m /min every two weeks until they finally reached 60 minutes per day and 18 m / min. For each training session, 5 minutes of warm-up with a speed of 5 to 10 m/min, and the same amount was considered for cooling-down.

In this device, in order to force the exercise and run, the body was hit with a wall or electric shock. Exercise was done in the morning between 9 and 12 o'clock. Rats that did not intervene were also taken to the gym and walked for 5-10 minutes on a treadmill at a low speed of 5 m / min.

**Table 1**. Numerical display of sport protocol in different weeks

| Weeks | 1st | 2nd | 3rd | 4th | 5th | 6th | 7th | 8th |
|---|---|---|---|---|---|---|---|---|
| Exercise time (minutes) | 10 | 10 | 20 | 30 | 40 | 50 | 60 | 60 |
| Rotation speed (meters per minute) | 5 | 5 | 10 | 10 | 15 | 15 | 18 | 18 |

***How to treat with curcumin*:**

Curcumin (purchased from Merk Kimia) was administered daily at a dose of 50 mg /kg to animals for 8 weeks as a DMSO solution and orally.

***Doing experiments:***

Plasma leptin concentrations were measured using ELISA and Germany's Diagnostica Kit's method, and hepatic enzymes Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT) were measured using calorimetric and Germany's Diagnostica Kit's.

To analyze the research data, SPSS18 software and the one-way ANOVA method, then Tukey's post hoc test was used, and Kolmogorov–Smirnov test was used to determine whether the data distribution was normal.

All quantitative values in this study were shown as mean and standard deviation and p <0.05 was considered statistically significant.

## Results

The results of the present study, which examined the effect of 8 weeks of moderate-intensity aerobic exercise with and without the use of curcumin on the amounts of leptin and hepatic enzymes in aged rats, are shown in Figures 1 to 3.

According to Figure 1, the amount of leptin in the elderly control group increased significantly compared to the younger control group, and this increase was significant (p<0.001) and eight weeks of moderate aerobic exercise had a decreasing effect on leptin levels. Leptin levels were not significant in the control group, but in the curcumin + exercise group (p < 0.01) and the curcumin group (p < 0.001), leptin levels showed a significant decrease compared to the older control group.

On the other hand, the amount of the Aspartate aminotransferase (AST) enzyme, as shown in Figure 2, was not significantly different between the old control group and the young control group. But eight weeks of moderate intensity aerobic exercise combined with curcumin significantly reduced the amount of this enzyme compared to the old control group. However, no significant changes were observed in the exercise and curcumin groups compared to the old control group.

According to Figure 3, the amount of the Alanine aminotransferase (ALT) enzyme in the old control group increased compared to the young control, but this increase was not significant. Eight weeks of moderate-intensity aerobic exercise combined with curcumin intake significantly reduced the amount of this enzyme compared to the old control group (p < 0.02). In the exercise group and curcumin, we also saw a decrease in the amount of this enzyme, but this decrease was not significant. In other words, doing 8 weeks of moderate-intensity aerobic exercise and taking curcumin alone did not significantly change the amount of this hepatic enzyme in the study groups.

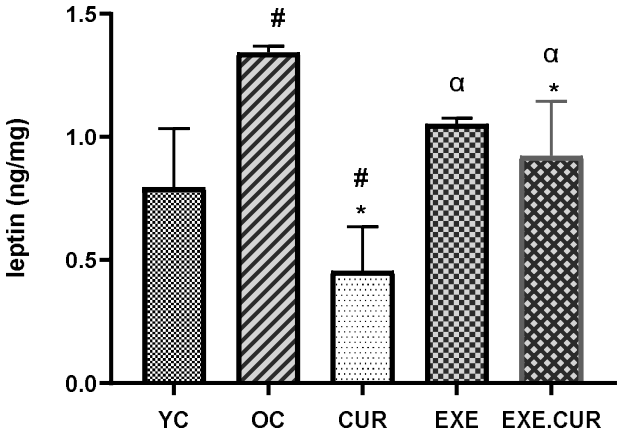


**Fig. 1.** The amount of leptin in 5 groups of study

Difference compared to the young control. *Denotes significant

Difference compared to the aged control. α Denotes significant

Difference compared to the curcumin group. †Denotes significant difference

Compared to the exercise group.

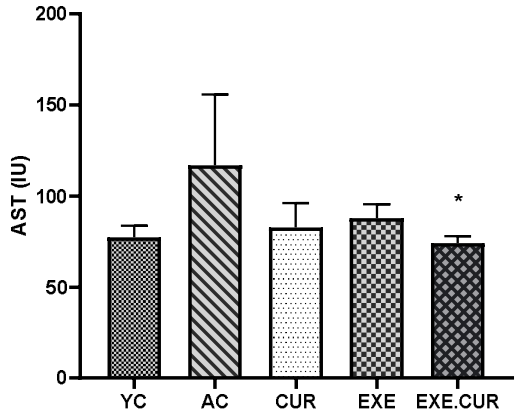


**Fig. 2**. The amount of AST in 5 groups of study

Difference compared to the young control. *Denotes significant

Difference compared to the aged control. α Denotes significant

Difference compared to the curcumin group. †Denotes significant difference

Compared to the exercise group.

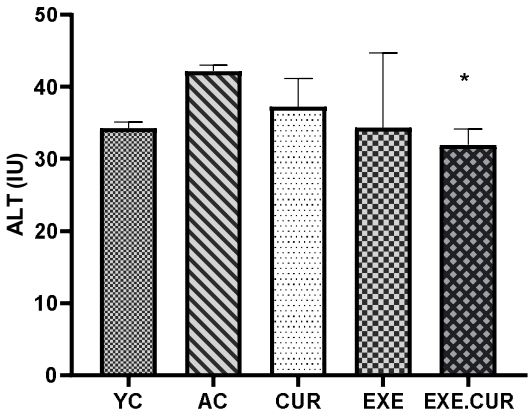


**Fig. 3**. The amount of ALT in 5 groups of study

Values represent the mean ± SEM (n=8). # Denotes significant

Difference compared to the young control. *Denotes significant

Difference compared to the aged control. α Denotes significant

Difference compared to the curcumin group. †Denotes significant difference

Compared to the exercise group.

## Discussion

Severe increases in plasma leptin levels, which are seen in elderly individuals, lead to leptin resistance (20), can be deposited in the liver, and cause steatosis and non-alcoholic fatty liver (2). The present study was conducted for the first time to investigate the effect of 8 weeks of moderate-intensity aerobic exercise and curcumin use alone and in combination with Aspartate aminotransferase and Alanine aminotransferase enzymes as well as leptin levels.

Findings from this study indicate the significant effect of moderate-intensity aerobic exercise and consumption of curcumin supplementation in reducing the amounts of hepatic Aspartate and Alanine

aminotransferase enzymes in the old group. Each alone has not been able to significantly reduce these hepatic enzymes (21).

The findings show that aerobic activity alone does not significantly change leptin levels. Along with these results, Kraemer et al. did not observe significant changes in leptin levels in obese women after 9 weeks of aerobic exercise (22). Also, Houmard et al. did not show any changes in leptin levels after 7 days of aerobic exercise with a maximum intensity of 75% consumed oxygen (23). These studies stated that aerobic exercise alone could not reduce leptin levels. Contrary to current research, Hayase et al. found that swimming exercise for ten weeks at 60 percent maximum oxygen consumption for one hour and twice a week significantly reduced serum leptin levels in women. They found a strong correlation between reduced body fat and reduced leptin levels (24). Miyatake et al. examined overweight men who did aerobic exercise for one year and three sessions a week by 65 percent of their maximum oxygen intake and 50 minutes per session. They found a significant reduction in leptin levels without a decrease in body fat percentage and body mass index. They attributed this decrease to insulin because insulin sensitivity had improved after exercise (25).

However, the two factors of reducing body fat percentage and increasing insulin sensitivity can be considered as effective factors in reducing leptin levels after aerobic exercise, and the reason for the lack of significant reduction in our study could be due to low-intensity and duration of exercise. On the other hand, taking curcumin supplement alone for 8 weeks could significantly reduce the amount of leptin in the elderly group.

The results were consistent with the findings of Wong Jong et al. They treated subjects with a high-fat diet, and a high-cholesterol diet, with 2.5 and 5 percent turmeric extract supplement, and found a significant reduction in leptin levels. Turmeric curcumin can regulate leptin levels by controlling fat metabolism. Curcumin can also regulate energy metabolism and reduce body fat levels. (26). Also, aerobic activity and combined use of curcumin have significantly reduced the amount of leptin, which can be attributed to curcumin due to the results of exercise and consumption of curcumin alone. On the other hand, in our study, 8 weeks of moderate aerobic exercise and curcumin supplementation alone were not able to significantly reduce the levels of the Aspartate aminotransferase and Alanine aminotransferase enzymes, but together they significantly reduced the levels of these enzymes.

In line with the results of our study, Navekar et al. (27) and Moradi et al. (28) did not observe significant changes in the values of the two hepatic enzymes mentioned following the use of curcumin supplementation. Controlling and reducing the amounts of these hepatic enzymes are indicated. Among them is the study of Panahi et al. In which 8 weeks of taking curcumin at a dose of 1000 mg per day in patients with NAFLD significantly reduced hepatic enzymes (29).

The anti-inflammatory property of curcumin is due to the fact that it inhibits the production of TNF-α (Tumor necrosis factor-alpha) and IL-1 (interleukin-1), which is a precursor to cytokines and prevents the synthesis of NO (Nitric oxide). Although the anti-inflammatory mechanisms of curcumin are not fully understood, recent studies have shown that curcumin inhibits the inflammatory pathway of the JAK-STAT signal and inhibits the phosphorylation of STAT1 and STAT3 in microglia activated by gangliosides and interferon Ɣ. (30). It also inhibits the binding of monocytes to human epithelial cells. (31) Curcumin also significantly inhibits the production of inflammatory cytokines by monocytes induced by LPL (32).

Oxidation of fatty acids decreases due to aging and decreased ability of the liver, which increases lipogenesis and accumulation of fat in the liver and inflammation (33). On the other hand, the blood flow to the liver and the volume of the liver and the number of mitochondria decrease with the number of mitochondria at the age of 20-70 years (34). So, it can be concluded that taking curcumin supplementation due to its antioxidant and anti-inflammatory properties can play a positive role in reducing hepatic damage. However, in the present study, this effect was not significant, and it may be possible to benefit from useful effects of

curcumin by changing the length of the course of supplementation with curcumin or the used dose. This requires further research.

On the other hand, 8 weeks of moderate aerobic exercise did not show significant changes in the levels of AST and ALT enzymes, which contradicts with the findings of studies by Shamsoddini et al. They showed that 8 weeks of aerobic exercise significantly reduced these enzymes. (13) Also, the research of Farzengi et al. showed the positive effect of aerobic exercise on the values of hepatic trans-aminases in postmenopausal women. In this study, low-intensity exercise due to less stress improved the amounts of hepatic enzymes because the number of hepatic enzymes can change due to the intensity, duration, and type of exercise (35).

Haus et al. reported that endurance exercise by targeting liver fat reduces the risk of developing NAFLD. Improved liver fat is likely due to increased adiponectin, fat oxidation, and increased insulin sensitivity (36). Hallsworth et al. also described the basic mechanisms of changes in liver fat due to exercise as a result of changes in insulin sensitivity, circulatory fats, and energy balance (37).

In our study, 8 weeks of moderate-intensity aerobic exercise and supplementation with curcumin were able to significantly reduce the levels of these two hepatic enzymes, which suggests that the two components of exercise and curcumin together can have positive effects on reducing side effects of NAFLD and the reason for the lack of significant effects of any components of exercise and curcumin supplementation alone can be due to the intensity and short duration of exercise or low doses of curcumin.

## Conclusion

8 weeks of aerobic exercise did not significantly change the mean intensity of liver and leptin enzymes. On the other hand, taking curcumin supplements for 8 weeks did not significantly reduce hepatic enzyme values, but did significantly reduce leptin levels.

Concomitant use of curcumin and aerobic activity was able to significantly reduce the amounts of hepatic enzymes and leptin in older rats. These results can be used in the field of medicine and the treatment of patients and require further studies.

## Acknowledgments

This work derived from a Ph.D. thesis in Exercise Physiology at Urmia University, Urmia, Iran.

## Funding source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## Conflict of interest

The authors declare that they have no conflict of interest.

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