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Randomized Clinical Trial

The Effect of Aerobic-resistance Training and Caloric Restriction on Hepatokine Factors Alterations in Obese Women with Non-alcoholic Fatty Liver Disease

Mitra Hayati[1], MSc; Fardin Fatahi[1*], PhD; Abdolhossein Taheri Kalani[1], PhD

[1]Department of Exercise Physiology, Il.C., Islamic Azad University, Ilam, Iran

*Corresponding author: Fardin Fatahi, PhD; Student Blvd, Islamic Azad University, Postal code: 69311-33145, Ilam, Iran. **Tel:** +98-84-32226824; **Fax:** +98-84-32228075; **Email:** fatahi.fardin@gmail.com

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Abstract

Background: Factors secreted from hepatocytes, such as hepatokines, play a role in regulating intra and extrahepatic metabolic processes. The aim of this study was to investigate the effect of combined aerobic-resistance training (CT) and calorie restriction (CR) on hepatokines alteration in women with non-alcoholic fatty liver (NAFL) disease.
Methods: This quasi-experimental study was carried out using a pretest-posttest design in Ilam, Iran during the spring of 2023. A convenience sample of 37 participants was selected and randomly divided to one of four groups: control, CR, CT and CR+CT. The CT program was performed for eight weeks and three sessions per week. The CR groups, alleviate 400- 500 kcal/day from total daily calorie intake. Fatty liver was measured by ultrasound. Serum level of leukocyte-derived chemotaxin 2 (LECT2), angiopoietin-dependent growth factor (AGF) and sex hormone-binding globulin (SHBG) were measured in pre- and post-intervention. Analysis of covariance (ANCOVA) and Bonferroni post hoc test were used to analyze between-group alterations.
Results: After CT and CR+CT, LECT2 (P=0.011, P=0.006, respectively) and AGF (P=0.041, P=0.032, respectively) level significantly decreased than the control group, and in CR group decreased compared with the pre-intervention (P=0.037, P=0.018, respectively). Also, SHBG level in the CT and CR+CT groups significantly increased than the control group (P=0.013, P=0.006, respectively), and in CR group increased than the pre-intervention (P=0.004).
Conclusions: CR has limited effects on the level of hepatokines in obese women with NAFL disease. In order to create favorable alterations in the level of hepatokines, this intervention should be implemented with CT.

Keywords: Exercise training, Calorie restricted diet, Hepatokine, Hepatic steatosis

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1. Introduction

The accumulation of fat in liver tissue (hepatocytes) is called non-alcoholic fatty liver (NAFL) disease, which is associated with metabolic syndrome, cardiovascular diseases and type 2 diabetes (1). There is also an inverse relationship between the level of physical activity and NAFL disease. Recently, lifestyle behavioral interventions, such as regular physical activity, have been proposed to modulate NAFL (2). On the other hand, abdominal obesity and sedentary are independent risk factors for the occurrence of chronic diseases such as type 2 diabetes and NAFL (3).

Recent advances in genetic technologies have provided new insights into the role of the liver as a central endocrine organ in metabolism (4). In addition, growing evidence has shown that the liver mediates the metabolic regulation between the liver and other organs by secreting various factors, including hepatokines (5). Hepatokines are hormone-like proteins mainly secreted by liver cells, and their concentration is significantly impaired in NAFL. In fact, disruption of hepatokines secretion in the onset of NAFL may alter the inter-organ signaling and contributes to the development of complex and multifaceted metabolic disorders (6).

Hepatokines include fetoin A and B, sex hormone binding globulin (SHBG), angiopoietin-related growth factor (AGF), and leukocyte derived chemotaxin 2 (LECT2) (7). SHBG is produced in the liver and its main function is to transport sex hormones. However, SHBG serum concentration is also related to glucose metabolism, obesity and components of metabolic syndrome (8). It has been reported that serum SHBG concentration are lower in postmenopausal women with NAFL disease than in healthy controls (9). Likewise, the serum concentration of SHBG decreased with the increase of intrahepatic fat, and changing the lifestyle as a treatment for obesity, which resulted in the reduction of intrahepatic fat, increased the serum concentration of SHBG (10, 11). AGF, also known as angiopoietin-related protein 6, is encoded by the Angptl6 gene and mainly released by the liver into the bloodstream (12). Studies showed that obese mice had AGF deficiency, insulin resistance and lipid accumulation in the liver and skeletal muscles (13). Therefore, this hepatokine may play an important role in carbohydrate and fat metabolism, and is considered as a protein that fights obesity and insulin resistance (12). LECT2 is another hepatokine expressed by liver cells in obese and insulin resistant individuals (14). In a previous study, it was shown that LECT2 expression in the liver is higher following a high-fat diet (15). Deletion of LECT2 in mice improves insulin sensitivity, which highlights its role in metabolic disorders. Treatment with recombinant LECT2 protein causes insulin resistance in skeletal muscles by disrupting insulin signaling (16). In experimental study, the AMP kinase enzyme is associated with negative regulation of LECT2 expression in the liver (17). Furthermore, human studies indicated that there is a direct relationship between serum LECT2 with BMI, waist circumference, HOMA-IR, and HbA1c (16, 18). It was also reported that the serum level of LECT2 is significantly higher in obese and NAFL patients (18).

Suggested treatments for NAFL include weight loss through diet, physical activity, and surgery in severe obesity. Although rapid weight loss aggravates this disease, but gradual weight loss has the greatest therapeutic effect on obese people with fatty liver (19). The most effective way to reach the ideal weight is to limit the intake of calories (20). Another effective way to control weight is exercise training, which helps maintain ideal weight by reducing appetite and adipose tissue mass (21). Also, exercise prevents damage to mitochondria and hepatocytes by increasing fatty acid oxidation, thus beneficially impacts the risk of onset and progression of chronic liver diseases (22, 23). However, there is limited evidence about the simultaneous effects of CR and exercise training on NALF disease. Based on the literature search, the effects of exercise intervention on the level of serum hepatokines have been investigated in only one study (24). In this study, 8 weeks of high intensity interval training (HIIT) in women with NAFL, decreased LECT2 and AGF and increased SHBG concentration (24). In addition, the interactive effects of exercise training and caloric restriction (CR) on serum hepatokines in patients with NAFL have not been considered. Therefore, this study aimed to investigate the impacts of eight weeks of combined aerobic- resistance training (CT) and CR on alterations in the serum concentration of LECT2, AGF and SHBG in women with NAFL.

2. Methods

2.1. Study design

This was a quasi-experimental study with a pre-test and post-test design.

2.2. Participants

The statistical population for this investigation consisted of all obese women with grade 2 and 3 NAFL residing in Ilam, Iran during the spring of 2023. The convenience sample was selected based on predetermined inclusion and exclusion criteria. The G*Power software (α=0.05, power=0.95), was used to calculate the sample size based on the AGF variable (25). The mean and standard deviation values for the experimental and control groups were 6.29±1.08 and 7.81±1.35, respectively. The inclusion criteria were: not taking any medication, having no chronic disease and no physical activity a year before the beginning of the study, having an appropriate level of physical and mental health. The exclusion criteria were: non-compliance with recommended matters during the study, not regularly implementing the training program, changing the diet, history of cardiovascular, metabolic and kidney diseases, cancer, hypertension, hormonal disorders, and incidence of disease during the intervention. All the participants received information about the study and after reviewing this information, they were asked to sign the written informed consent. All the participants completed the related questionnaires and had no blood pressure, diabetes, and kidney and liver diseases. In addition, in one session, the participants became familiar with the methods of exercise.

All conditions, limitations, disadvantages, benefits and side effects of the interventions in the present study, including CR and CT or their combination (CR+CT) were explained to the participants. Finally, 37 obese women (age: 33.5±3.2 years; body mass: 83.7±7.1 kg; Body mass index (BMI): 34.1±4.2 kg/m^2) with NAFL, who attended medical centers in Ilam, Iran were selected. The study participants were randomly assigned to one of the four groups: control (n=9), CR (n=9), CT (n=9) and CR+CT (n=10). For random allocation, the participants randomly chose a number ranging from 1-37 (1-9 for the control, 10-18 for CR, 19-27 for CT, and 28-37 for CR+CT groups) from a bag containing the numbers. CONSORT flow diagram is presented in Figure 1.

2.3. Interventions

To ensure precise management of dietary intake throughout the study, a nutritionist closely monitored all participants. A 24-hour dietary recall questionnaire was used to determine energy intake during one week before and one week after the intervention (two normal days and one day off). To fill up the forms correctly, all the participants were given information about how to fill the questionnaire, units of measurement and choosing suitable days. The mentioned amounts of food were converted into grams using manual kitchen scales, and then coding was done according to the instructions of the N4 diet analysis software, and the amount of energy and macronutrients received was calculated. For each participant, 400- 500 kcal were deducted from the average energy intake for three days, and the diet was designed with the following distribution: 55- 60% carbohydrate, less than 30%bfat, and 10- 15% protein. The balanced low-calorie diet was based on the list of substitution tables (26), and after presenting the diet, explanations about the food pyramid, participation of each food group, restrictions on the amount and time of eating food, and the substitution appropriate solutions were provided for each participant.

Before starting training programs, all participants became familiar with the training procedures, intensity and equipment. The CT program was conducted three sessions per week for eight weeks (27).

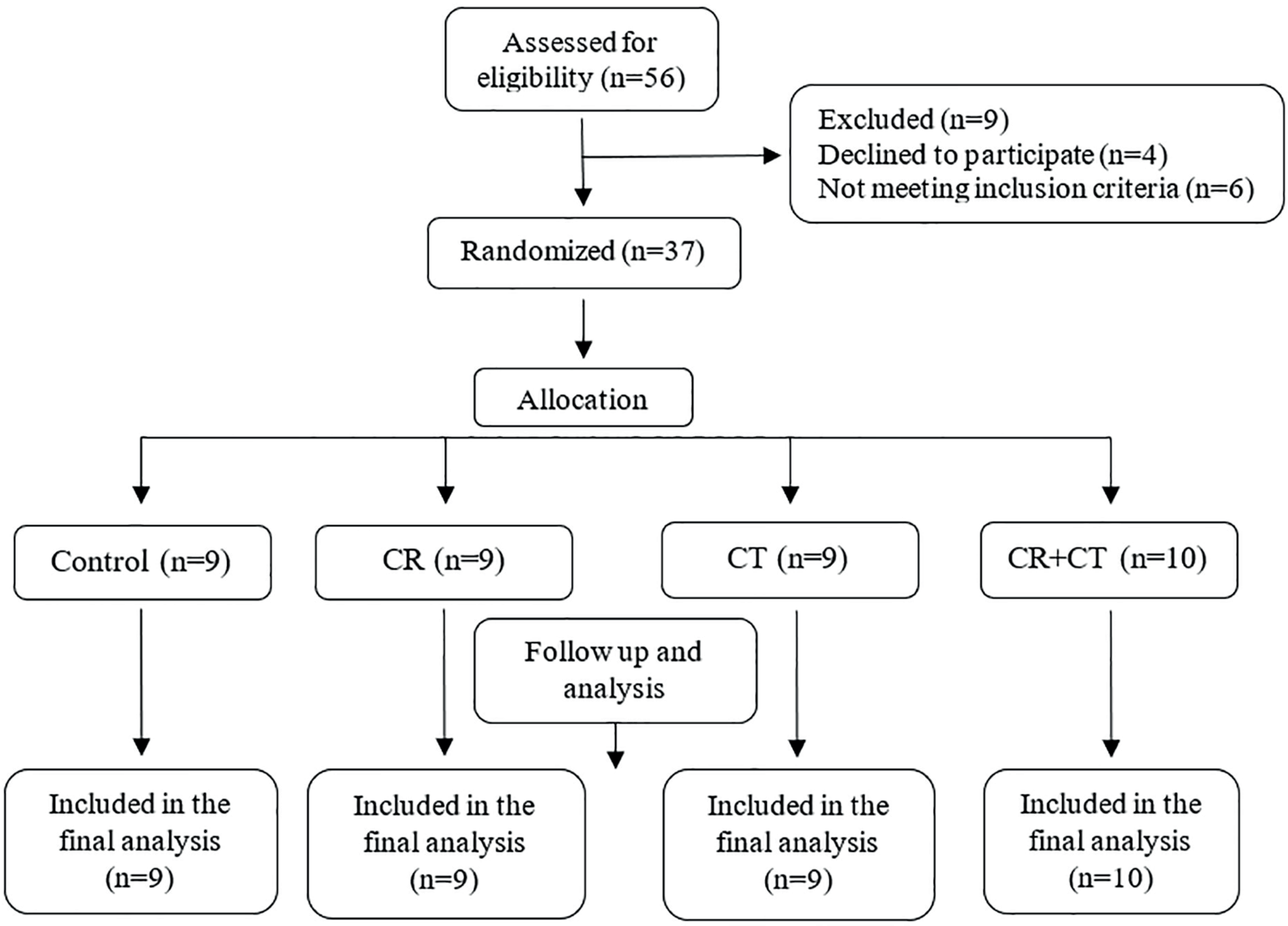

Figure 1: The figure shows the CONSORT flow diagram. CR: Caloric Restriction; CT: Combined Aerobic- resistance Training

The aerobic part of the training consisted of 20 minutes of continuous running with an intensity of 40% of the heart rate reserve (HRR) in the first and second weeks, which was increased for 5 minutes every two weeks and 5% of its intensity so that at the end of the 8th week, it reached 30 minutes with an intensity of 60% of HRR. The resistance part of the training consisted of performing eight exercises (lunge, leg flexion, leg extension, calf raise, bench press, lat pull-downs, trunk extension, sit-up) in the first week with 40% of one maximum repetition (1RM) in 3 sets of 10-12 repetitions were performed with a 90-second rest between each set and exercise. Every two weeks, 5% was added to the training intensity and at the end it reached 60% of 1RM in 3 sets and with 8-10 repetitions in the eighth week. When the participant was able to perform 2 additional repetitions in each set, resistance was added in the next set. At the end of the fourth week, 1RM was recalculated and the resistance training program for the following weeks was designed based on the new 1RM.

A 5-minute warm-up at the beginning and a 5-minute cool-down was performed at the end of each training session. The participants of the control group did not participate in any exercise program during the study period and continued their normal life.

2.4. Measurements

The height and body mass of the participants were measured and recorded using a medical scale (Saca, Germany). BMI was calculated as body mass (kilograms) divided by height (meters) squared. The participant's waist was measured midway between the lowest rib and the iliac crest. The hip circumference was measured using a flexible two-meter standard tape measure at the point of maximal gluteal protuberance from the lateral view. The waist-to-hip ratio (WHR) was then calculated. Body fat mass was determined by bioelectrical impedance analysis using a Body Composition Analyzer (Tanita– BC418, Japan).

In this study, ultrasound was used to diagnose NAFL. Before the start of the study and 48 hours after the last training session, the participants underwent an abdominal ultrasound using a GE Voluson 730 (USA). NALF disease was classified as mild, moderate, and severe grades 1, 2, and 3, based on the echogenicity of liver, respectively.

After a 12-hour overnight fast and eight hours of sleep, blood samples were taken from the antecubital vein to measure serum concentration of LECT2, AGF, and SHBG in pre- and post-intervention. Post-intervention blood samples were obtained from participants in the training groups, 3 days after their last exercise session. On the days before the blood samples were taken, the participants were asked to avoid strenuous exercise and taking any drugs or supplements for 3 days. To prevent the effect of circadian rhythm, blood samples were taken at a certain time of the day between 08:30 and 09:30. AGF and SHBG (ELISA kits, Hangzhou Eastbiopharm Co, USA), and LECT2 (ELISA kits, biovendor, USA) were analyzed by commercially available enzyme-linked immunosorbent assay. The intra- and inter-assay coefficients of variation for cytokines were <5%.

2.5. Data Analysis

Data were reported based on Mean±Standard Deviation. Statistical analysis of the obtained data was performed via SPSS version 24. The Shapiro-Wilk test was used to determine the normality of data distribution and Levene's test was used to examine the homogeneity of variances ($P>0.05$). The mean values before and after the interventions were compared using the paired t-test. Also, the differences in variables between the four groups (control, CR, CT and CR+CT) were compared with the analysis of covariance (ANCOVA), and then post hoc Bonferroni was used to compare pairwise means. The level of significance was considered to be $P<0.05$ for all the tests.

3. Results

Table 1 shows the demographic and anthropometric characteristics of the participants in pre- and post-intervention. At the beginning of the study, the analysis of covariance did not reveal any significant difference in anthropometric characteristics indices between the four groups (in all, $P>0.5$). But at the end of the intervention, waist circumference in the CR, CT and CR+CT groups significantly decreased than the control ($P=0.02$, $P=0.03$, and $P=0.01$, respectively). The body fat percentage in the CR+CT group as compared with the control group ($P=0.02$) and that in the CR and CT groups significantly decreased according to the pre-intervention ($P=0.02$ and $P=0.04$, respectively). A significant decline was seen in BMI in the CR

Table 1: The demographic and anthropometric characteristics of the participants in pre and post-intervention					
Variables	**Groups**				**Between- group Differences (P value)**
	Control	**CR**	**CT**	**CR+CT**	
Age (years)					
Pre-intervention	33.5±2.9	32.6±2.8	34.1±3.7	33.8±3.6	0.614
Body mass (kg)					
Pre-intervention	81.8±7.6	84.2±9.3	82.9±5.2	85.6±6.3	0.02
Post-intervention	82.1±7.9	82 ±8.5*	81.6±6.6	80.8±6.1#	
Within- group Differences (P value)	0.87	0.03	0.56	0.01	
BMI (kg/m^2)					
Pre-intervention	32.9±3.6	35.1±4.7	33.8±3.9	34.5±4.8	0.03
Post-intervention	33±3.7	34.2±5*	33.4±4.1	32.8±5.2*	
Within- group Differences (P value)	0.92	0.04	0.89	0.04	
Body fat percentage (%)					
Pre-intervention	38.4±3.5	35±3.3	40.2±3.8	37.2±3.6	0.01
Post-intervention	38.1±3.3	33.7±4.1*	38.6±3.7*	34.9±3.4#	
Within- group Differences (P value)	0.75	0.02	0.04	0.01	
Waist circumference (cm)					
Pre-intervention	108.4±10.2	105.8±8.7	110.3±11.4	106.7±9.8	0.01
Post-intervention	108±9.8	101.5±9.3#	104.7±10.1#	98.4±8.6#	
Within- group Differences (P value)	0.94	0.02	0.01	0.01	

Data are expressed as mean±standard deviation. *Significantly decrease compared to the pre-intervention. # Significantly decrease rather than control group. CR: Caloric Restriction; CT: Combined Aerobic- resistance Training; BMI: Body Mass Index.

Table 2: Serum hepatokines alterations in pre and post-intervention in the study groups					
Variables	**Groups**				**Between- group Differences (P value)**
	Control	**CR**	**CT**	**CR+CT**	
LECT2 (ng/ml)					
Pre-intervention	4.1±0.76	3.9±0.65	4.2±0.81	4±0.73	0.009
Post-intervention	4.2±0.79	3.4±.0.61*	3.5±0.67#	3.2±.0.58#	
Within- group Differences (P value)	0.72	0.037	0.001	0.001	
AGF (ng/ml)					
Pre-intervention	7.2±1.6	7.4±1.2	6.8±1.1	7.3±1.8	0.03
Post-intervention	7.1±1.3	6.8±0.9*	5.9±0.8#	6.1±0.7#	
Within- group Differences (P value)	0.65	0.018	0.011	0.009	
SHBG (ng/ml)					
Pre-intervention	21.8±4.6	25.7±5.2	26.5±6.1	28.3±5.5	0.007
Post-intervention	22.4±4.8	29.8±5.9*	32.1±7.2#	35.2±6.7#	
Within- group Differences (P value)	0.84	0.004	0.002	0.001	

Data are expressed as mean±standard deviation. *Significantly difference compared to the pre-intervention. # Significantly difference rather than the control group. CR: Caloric Restriction; CT: Combined Aerobic- resistance Training; LECT2: Leukocyte derived chemotaxin 2; AGF: Angiopoietin-related Growth Factor; SHBG: Sex Hormone Binding Globulin.

and CR+CT groups as compared with the baseline (P=0.04; P=0.04). Also, body mass decreased significantly in the CR+CT groups than the control (P=0.02) and in the CR compared with the pre-intervention (P=0.03).

Alterations in the serum level of hepatokines before and after the intervention in the experimental and control groups are presented in Table 2. The results of covariance analysis and Bonferroni's post hoc test showed a significant decrease in LECT2 and serum AGF concentration in CT (P=0.011 and P=0.041, respectively) and CR+CT (P=0.006 and P=0.032, respectively) groups as compared with the control group, and in CR compared with the pre-intervention (P=0.037, P=0.018, respectively). Additionally, a significant increase was seen in the concentration of serum SHBG in the CT (P=0.013) and CR+CT (P=0.006) groups compared with the control group, and in the CR group when compared with the pre-intervention (P=0.004).

4. Discussion

The findings of present study revealed that eight weeks of CT alone or in combination with CR results in a significant reduction in the circulation concentration of LECT2 and AGF that the control group, and in CR group decreased rather than the pre-intervention. Moreover, the increase in SHBG concentration in the CT and CR+ CT groups was significant that the control, and in CR compared to the pre-intervention.

In the present study, CR, CT and CR+ CT decreased LECT2 concentration in obese women with NAFL. There are very limited studies on the effect of exercise training and diet interventions on LECT2 (24, 28). Only one study reported a significant decrease in LECT2 level in women with NAFL following eight weeks of HIIT (24).

It has been reported that LECT2 serum concentration is positively correlated with the severity of NAFL, insulin resistance, inflammation and liver fibrosis (29). In addition, high-fat diet increased serum and liver LECT2 level in both animal and human models (30). On the contrary, following exercise training or pharmacological inhibition of dipeptidyl peptidase-4 in mice, the level of LECT2 decreased, which was attributed to the increase in AMPK phosphorylation (28). Also, M1 type macrophages and lower M1/M2 ratio were reported in the liver of mice with LECT2 deficiency, which was associated with a decrease in liver inflammation (31). According to this finding, LECT2 plays a role in the onset of NAFLD. Given the possible reduction of intrahepatic fats and NAFL grade in the study participants, the decrease of LECT2 concentration seems reasonable. Therefore, according to our results, CT with and without CR can help improve patients with NAFL by reducing LECT2 concentration. At the same time, CT is more effective than CR in reducing LECT2 serum concentration.

The reduction of AGF level following CT and CR+ CT in obese women with NAFL was another finding of the present study. Human studies in this field are limited, but a few research are consistent with the present study. For example, a decrease in serum AGF concentration was reported in women with NAFL following eight weeks of HIIT (24). Literature showed that angiopoietin-related growth factor (AFG/Angptl6) effectively regulates fat, glucose and energy metabolism (32-34). It has been reported that AGF can be a potential regulator of metabolism homeostasis by combating obesity (32). On the other hand, it has been suggested that the overexpression of AGF in mice causes interference in the use of glucose and a decrease in hepatic glucose metabolism through insulin (33). Similarly, in AGF-deficient mice, glucose tolerance improved, fat mass increased, and visceral fat and inflammation decreased (34). Thus, it can be concluded that CT with CR exerts beneficial effects on glucose and fat metabolism by modulating AGF concentration and helps to improve NAFL.

On the other hand, some studies yielded findings that were inconsistent with those of the present study. Ingerslev and colleagues showed that AGF mRNA expression increased after a 60-minute ergometer cycling exercise in human participants (32). Also, a session of aerobic exercise (two hours/ cycling with an intensity of 50% of maximal oxygen consumption) increases the level of circulating AGF during fasting in healthy adults (35). These studies (32, 35) examined the acute effects of exercise and may be the reason for the discrepancies between their results and the findings of the present study. It seems that the changes of AGF to acute and chronic exercise are different. However, more controlled studies are needed to make a definitive statement.

Finally, the results of the present study showed that the concentration of SHBG increased significantly following CT and CR+ CT. It was reported that the level of SHBG increases with changes in lifestyle, including diet and aerobic exercise, and its increase is related to the reduction of steatosis (36). Consistent with our study, some other studies (24, 37, 38) reported an increase in SHBG concentration following different models of aerobic training. It was shown that after eight weeks of HIIT, serum concentration of SHBG increased in women with NAFL (24). Similarly, 16 weeks of aerobic training increased SHBG concentration in obese women (37). In another study, daily walking along with CR for three weeks increased serum SHBG level in obese men (38). Similar characteristics of the participants, such as gender, body composition, and health status, as well as the type of exercise intervention, may be regarded as the reason of the alignment of these results.

The mechanisms of SHBG increase following exercise-diet interventions are not fully understood.

In this regard, due to the inverse relationship between BMI and SHBG level, it is possible that the improvement in the level of this hepatokine is due to the change in body composition and the reduction of body fat percentage (39). In confirmation of this hypothesis, along with an increase in SHBG level, a decrease in body fat percentage and BMI has been seen in the present study. Decreased insulin level is another proposed mechanism for increasing SHBG. Also, according to experimental findings, adiponectin upregulates SHBG production in liver cells (39). Since the insulin and adiponectin concentration was not measured in our study, no definite conclusion can be made in this regard. To understand the exact mechanisms of SHBG level changes following training and CR, further research is warranted.

Inconsistent with our result, in another study, SHBG concentration did not change after 10 weeks of CT in obese postmenopausal women (40). The possible reason for these contradictory results may be due to the difference in the type, intensity, and duration of exercise used and the characteristics of the participants.

4.1. Limitations

This study had certain limitations. Firstly, the genetic characteristics, level of physical activity outside the study time, amount of sleep and menstrual cycle of the participants could not be controlled, as these factors may affect individual adaptations to the used interventions. Secondly, some factors affecting the level of hepatokines, such as insulin and adiponectin, were not measured in this study. Additionally in this study, only obese women with NAFL were used, which potentially limiting the generalizability of the findings to other populations.

5. Conclusions

In summary, the results of the present study revealed that combined aerobic- resistance training independently and with caloric restriction improves the level of hepatic hepatokines and the body composition of patients with NAFL. Also, combined aerobic- resistance training more effectively than caloric restriction changed the concentration of serum hepatokines. Caloric restriction has limited effects on the level of hepatokines in obese women with NAFL disease. In order to create favorable alterations in the level of hepatokines, this intervention should be implemented together with combined aerobic- resistance training. However, due to the lack of sufficient data in this field, further research is needed to achieve a general result, and the effective mechanisms on liver hepatokines in patients with NAFL.

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Authors' Contribution

Mitra Hayati: Substantial contributions to the conception and design of the work; the acquisition, analysis, and interpretation of data for the work; drafting the work and reviewing it critically for important intellectual content. Fardin Fatahi: Substantial contributions to the conception and design of the work; the acquisition, analysis, and interpretation of data for the work; drafting the work and reviewing it critically for important intellectual content. Abdolhossein Taheri Kalani: Substantial contributions to the conception and design of the work; the acquisition, analysis, and interpretation of data for the work; drafting the work and reviewing it critically for important intellectual content. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work, such as the questions related to the accuracy or integrity of any part of the work.

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Ethical Approval

This study was approved by the Ethics Committee of Sport Sciences Research Institute of Tehran, Iran with the code of IR.SSRC.REC.1402.106. Also, written informed consent was obtained from the participants.

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