Gastroenterology and Hepatology From Bed to Bench.
2023 **RIGLD**, Research Institute for Gastroenterology and Liver Diseases

ORIGINAL ARTICLE

The role of moderate- and high-intensity supervised aerobic training in reducing steatosis and hepatic fibrosis in patients with non-alcoholic fatty liver disease; a randomized controlled trial

Mohammad Hassabi[1,2], Amir Sadeghi[3], Amir Hosein Abedy Yekta[1,2], Shahin Salehi[1,2], Behnaz Mahdaviani[4], Ahmadreza Asgari[5], Mehrshad Poursaeid Esfahani[1,2]

[1] Taleghani Hospital Research Development committee, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2] Department of Sports and Exercise Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[3] Gastroenterology and Liver Diseases Research Center, Research Institute for Gastroenterology and Liver Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[4] Sports Medicine Research Center, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran
[5] School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

ABSTRACT

Aim: This study aimed to compare the effect of the same volume of moderate- and high-intensity aerobic exercise on patients' liver steatosis and fibrosis.

Background: Exercise is known strategy to deal with non-alcoholic fatty liver disease (NAFLD).

Methods: This Randomized Control Trial was performed on 60 patients randomly assigned to three arms of the study (1:1:1). Fibrosis and steatosis of liver including Control Attenuated Parameter (CAP) determined using Transient Elastography (TE). The control group was advised to adjust their lifestyle, as a routine management. The intervention groups additionally, participated on supervised exercise programs with two different intensities but the same volume of 1000 KCal per week. The intensities of 50% and 70% of V02 reserve were considered for moderate-intensity and vigorous programs, respectively.

Results: On six-month follow-up, none of outcomes were statistically significant among three arms of study. However, changes in some outcomes were reached to statistically significant difference in follow-up in comparison with baseline. The mean of CAP score changes was -19.43 (31.43) (P=0.03), 9.92 (26.81) (P=0.21), and 14.61 (18.03) (P=0.01) in control, moderate- and high-intensity groups, respectively. In the high-intensity group, in addition to steatosis, this difference was also observed in the rate of fibrosis. Besides, the level of serum aminotransferases in the group with moderate exercise after six months had a significant decrease compared to baseline. (P=0.01)

Conclusion: Improvement in steatosis and fibrosis was more evident in high- intensity group. As the rate of drop out was high, caution is needed in interpretation of the results.

Keywords: Exercise, Non-alcoholic fatty liver disease, Fatty liver.

(Please cite as: **Hassabi M, Sadeghi A, Abedy Yekta AH, Salehi S, Mahdaviani B, Asgari A, Poursaeid Esfahani M. The role of moderate and high intensity supervised aerobic training in reducing steatosis and hepatic fibrosis in patients with non-alcoholic fatty liver disease; a randomized clinical trial. Gastroenterol Hepatol Bed Bench 2023;16(1):509-519. https://doi.org/10.22037/ghfbb.v16i1.2466).**

Introduction

Non-alcoholic fatty liver disease (NAFLD) has been defined as the accumulation of fat in the liver in the absence of alcohol consumption or any other specific causes. It is known as the most common chronic liver disease worldwide (1). The global prevalence of NAFLD was estimated to be 24%. This number varied across continents and was 27% in Asia (2).

Received: 14 August 2022 *Accepted*: 09 October 2022
Reprint or Correspondence: **Mehrshad Poursaeid Esfehani,** *Taleghani Hospital Research Development committee, Shahid Beheshti University of Medical Sciences, Tehran, Iran.*

E-mail: mpoorsaid@yahoo.com
ORCID ID: 0000-0003-0290-425X

Fatty liver disease ranges from simple steatosis to non-alcoholic steatohepatitis (NASH). In all cases the risk of cirrhosis is increased due to fibrosis (3). The increasing prevalence of NAFLD in adults, adolescents, and children appears to be a serious threat. (4) Obesity, insulin resistance, diabetes mellitus type 2, and hyperlipidemia are known risk factors of NAFLD (5). Therefore, its prevalence in obese and diabetic people reaches 70% and 90%, respectively (6).

Currently, worsening the obesity epidemic in the world has led to increase in the prevalence of NAFLD (7).

Early treatment is known as the most cost-effective approach in this regard. As the early diagnosis is mandatory for early treatment (8), the importance of diagnostic methods cannot be overstated.

Several methods have been used to diagnose hepatic steatosis. On the one hand, liver ultrasound is the easiest and most accessible of these methods but on the other hand (9), ultrasound cannot show steatosis less than 30%. Also ultrasound is a highly operator-dependent modality (6, 10). According to the American Association for the Study of Liver Disease (ASSLD), the gold standard for diagnosing NAFLD is biopsy (6). Due to the difficulty of performing a liver biopsy and its invasiveness and complications such as the risk of bleeding, the use of Transient Elastography (TE) as a non-invasive method is a practical solution in this regard (11, 12).

Use of indices is another non-invasive method for estimating liver fibrosis. These indexes are obtained through the introduced formulas using clinical and laboratory findings. FIB-4 is recognized as one of the best indices for estimating fibrosis in NAFLD patients (13).

Although there are significant limitations in pharmacological and surgical treatments in NAFLD, recent studies have shown that lifestyle intervention including activity could have a significant effect in this area (8).

Several studies have supported the benefits of aerobic training. It is thought aerobic exercise is responsible for reducing hepatic fat component within the range of 3-40% (9).

It is likely exercise induces fatty acid beta-oxidation, hepatic autophagy, PPAR-y pathway, as well as, insulin sensitivity, and reduces intrahepatic fat accumulation. Furthermore, increase in anti-inflammatory molecules, and anti-oxidant enzymes via exercise could lead to a reduction in ROS and OS generation during NAFLD progression (9).

Researchers declare that sedentary behavior among obese individuals increases the risk of developing NAFLD compared with active peers. These results support the theory of the positive effect of increasing the level of physical activity and exercise on NAFLD, and it seems that exercise is a good and inexpensive way to prevent and treat NAFLD (7).

One of the main challenges in this field is related to the proper amount of exercise (including intensity and volume) to effectively reduce liver fat content. However, what is certain is that aerobic and strength training, even in the absence of weight loss, can play a pivotal role in treating NAFLD (14).

This study aimed to evaluate the effect of the same volume of moderate- and high- intensity aerobic exercise on patients' liver steatosis and fibrosis.

Methods

This parallel RCT was performed on 60 patients with NAFLD randomly assigned to three groups of 20 people. Patients were followed for six months.

Adult patients with NAFLD who had been confirmed by clinical, laboratory, and imaging tests (TE) were selected on the basis of the following criteria; no other liver disease or any chronic disease that affects the function or histology of the liver, had not a previous history of regular exercise before the start of treatment.

All patients referred to the gastrointestinal clinic of Taleghani Hospital during the years 2018-2019, who were eligible, were offered to enter the study. Written informed consent was obtained from all included patients and then they were referred to the sports medicine ward of Taleghani hospital.

The protocol of this study is based on the principles of Helsinki and has been accepted in the ethics committee of Shahid Beheshti University of Medical Sciences under the number of IR.SBMU.MSP.REC.1395.252.

In the current study exclusion criteria were defined as follows; use of other treatments, refusal to continue study participation, refusal to perform paraclinical tests, the occurrence of any new disease that interferes with

the patient's tests, consumption of alcohol or other drugs that affect the liver, and diabetes.

Outcomes measurement

All Outcomes measured in the baseline, and after six months of follow up.

Anthropometric findings

Anthropometric assessment including height, weight, Body Mass Index (BMI), Waist Hip Ratio (WHR) were performed by one person.

Percentage of Body Fat (PBF)

In this study we use of BioImpedance Analysis (BIA) to determine body composition. PBF, fat free mass including skeletal bones, muscle mass, and total body water, are components that measured by BIA (15).

Cardiopulmonary exercise test

Cardio Pulmonary Exercise Test (CPET) was performed with Bruce modification protocol, and VO_2 Reserve (VO_2R) was measured.

Blood biochemistry

Biochemistry investigation were performed after 12 hours of fasting in the laboratory of Taleghani Hospital. Serum aminotransferases including Alanine Transaminase (ALT) and Aspartate Transaminase (AST), Ferritin levels, Lipid profiles (including High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL), Cholesterol, TriGlycerid (TG)), insulin resistance factors included Fasting Blood Sugar (FBS), fasting insulin level, HemoglobinA1c (HbA1c) were measured.

Liver steatosis and fibrosis

A liver TE was performed to determine fibrosis. To determine the degree of hepatic stiffness, the evaluation was performed by an experienced gastroenterologist using a standard protocol and a FibroScan device. In addition to estimating liver stiffness, liver TE can be used to quantify and approximate liver fat by measuring the Controlled Attenuation Parameter (CAP) score. It is measured based on ultrasound attenuation by intrahepatic fat at the central frequency of the TE probe (16). This score increases with increasing fat percentage and is known as an acceptable diagnostic method for steatosis detection.

FIB-4 index

It was introduced as a non-invasive fibrosis scoring method. According to the formula presented by Sterling

Table 1. Demographic and clinical characteristics of patients in the baseline.

Variable	Control (N=20)	Moderate intensity (N=20)	High intensity (N=20)	P value
Age (y)	49.85 (11.27)	53.20 (9.60)	47.55 (9.65)	.221
Sex (male/female)	11/9	11/9	11/9	1.000
Height (cm)	162.50 (7.74)	163.50 (8.70)	163.50 (9.85)	.918
Weight (Kg)	80.58 (11.98)	83.89 (16.16)	82.40 (17.45)	.793
BMI (kg/m2)	30.67 (5.30)	31.31 (4.74)	30.70 (5.34)	.905
Waist circumference (cm)	101.23 (8.11)	105.65 (14.52)	98.00 (10.02)	.171
Hip circumference (cm)	108.00 (8.62)	112.12 (14.10)	104.26 (6.69)	.118
WHR	0.79 (0.34)	.75 (.39)	.70 (.42)	.745
PBF (%)	32.83 (6.35)	33.71 (6.72)	31.91 (7.61)	0.716
Fibrosis	6.39 (1.93)	7.78 (2.42)	7.78 (2.55)	.101
Steatosis	296.65 (44.29)	303.15 (28.90)	290.50 (45.79)	.625
ALT (IU/L)	43.00 (19.06)	40.90 (21.16)	45.65 (23.55)	.781
AST (IU/L)	29.75 (13.99)	28.80 (10.19)	33.55 (20.58)	.595
Ferritin (ng/ml)	122.43 (80.77)	98.37 (80.41)	164.64 (84.50)	.095
FBS (mg.dl)	104.76 (23.24)	115.62 (25.87)	96.28 (11.49)	.064
A1c (%)	5.96 (1.47)	5.82 (1.15)	5.36 (1.01)	.392
Insulin (mIU/L)	12.29 (3.74)	17.14 (9.96)	11.62 (5.11)	.058
TC (mg/dl)	163.35 (29.01)	192.65 (49.99)	179.85 (32.22)	.060
TG (mg/dl)	186.85 (68.05)	162.10 (77.08)	180.35 (98.11)	.616
HDL (mg/dl)	38.35 (8.19)	44.73 (11.13)	45.68 (10.98)	.056
LDL (mg/dl)	96.50 (19.35)	120.84 (37.75)	99.52 (25.38)	.020*
Vo2max (ml/kg.min^{-1})	26.75 (4.76)	26.26 (6.22)	31.72 (7.50)	.022*
FIB-4	1.58 (0.68)	1.57 (.58)	1.52 (.63)	.971

Abbreviation

ALT: alanine aminotransferase, AST: aspartate aminotransferase, BMI: Body Mass Index, FBS: Fasting Blood Sugar, HC: Hip Circumference, HDL: High Density Lipoprotein, LDL: Low Density Lipoprotein, PBF: Percent of Body Fat, TC: Total Cholesterol, TG: Triglyceride, WC: Waist Circumference, WHR: Waist Hip Ratio * statistical significant.

et al. (17), this index was calculated by combining the routine serological factors such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), and platelet data, with age in the current study.

Randomization

Randomization was performed simply and individually. patients were grouped in groups of control, moderate-, and high-intensity groups, respectively.

Control group was only advised to adjust their lifestyle, including general recommendations for healthy eating, such as reducing dietary carbohydrate and fat intake and increasing physical activity. In intervention groups, in addition to nutritional recommendations similar to the control group, the exercise prescription was given according to the principles of FITT (Frequency, Intensity, Time, Type) (18). The FITT principles were introduced by American College of Sports Medicine (ACSM) order to provide a standard exercise prescription (19).

Exercise Prescription

In the current study, exercise prescription was determined as walking and walking on a treadmill with two different intensities but the same volume. The intended volume was 1000 kcal, and the average exercise intensity was 50% VO_2R for -moderate intensity group, and 70% of VO_2R for high intensity group. The frequency of exercise was considered five days a week, so that at least two days of it should be done under supervision in the sports medicine ward.

In people who were not physically fit at first, in the first one to two weeks, the exercise program started at a lower intensity and gradually increased to the desired level.

For home exercise sessions, the appropriate intensity was prescribed to the patient, according to the individual facilities and conditions of each patient, in the form of treadmill speed or the number of steps per minute based on the desired speed.

Statistical Analysis

Analysis of variance (one-way ANOVA test) was used to compare the baseline variables. To evaluate the comparison between groups and changes within groups, ANOVA and Paired-sample t-test were used, respectively. Analysis of covariance (one-way ANCOVA) were applied order to determine the

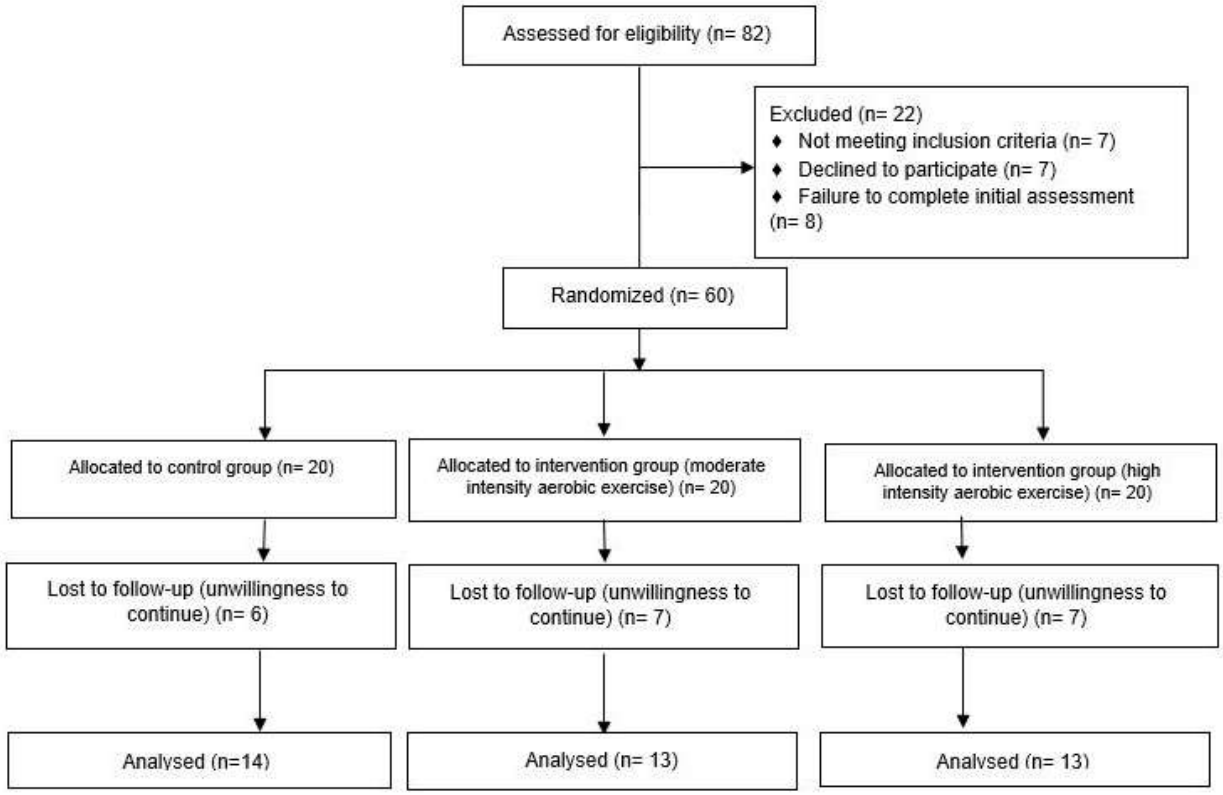

Figure 1. Flowchart of participants through the study.

baseline characteristics as covariates. For all analyzes, we used SPSS version 18 and defined the alpha error rate of 0.05.

Blinding

Due to the nature of the intervention, it was not possible to blind the participants. However, it was tried that the person who performs laboratory evaluations and TE examination, as well as statistical analyzer, to be unaware of the groups' assignment.

Results

Descriptive demographic variables are presented in Table 1.

In this study, 33 women and 27 men were randomized in three groups of 20 people.

The Figure 1 shows the flowchart of participants through the study. As can be seen 6, 7, and 7 participants were withdrawn from the study in control, moderate-, and high-intensity groups, respectively.

At baseline there was no significant difference between the groups in terms of gender, age, anthropometric findings (height, weight, BMI, WHR), and PBF (p-value > 0.05). Also as shown in Table 1, no differences in fibrosis, steatosis, and FIB-4 were observed between the study groups. The only differences between the groups in the baseline were their VO_2 Max (p-value = 0.03), and Low Density Lipoprotein (LDL). Consequently, the groups were not homogeneous in this respect.

According to Table 2, a paired t-test showed a significant decrease in steatosis after six months of follow-up in control group as well as high-intensity group. Changes in primary outcomes including FIB-4 index, fibrosis, and steatosis between before and after intervention by treatment arm have been shown in the Figures 2, 3, and, 4 respectively. The mean of CAP scores changes were -19.43 (31.43) (P=0.03), 9.92 (26.81) (P=0.21), and 14.61 (18.03) (P=0.01) in control, moderate- and high-intensity groups, respectively. In the high-intensity group, in addition to steatosis, this difference was also observed in the rate of fibrosis. The means of fibrosis changes were 0.03 (0.72) (P=0.85), -0.56 (1.54) (P=0.21), and -0.68 (0.82) (0.01) in control, moderate- and high-intensity groups, respectively. Besides, the laboratory findings of ALT, AST, and HbA1c in the group with moderate exercise after six months had a significant decrease compared to baseline (P=0.01, P=0.01, P=0.03).

A closer look at the data indicates that in both intervention groups, a decrease in anthropometric variables were observed. However, the results show that the greatest change in these findings were seen in the group with moderate exercise.

Table 3 shows the findings of the ANOVA analysis, which compared the mean of variables after six months between groups. Steatosis, fibrosis, and other anthropometric, and laboratory findings do not show a significant difference. The only significant measure was in the amount of VO_2 Max, which was seen in the baseline too. Considering baseline characteristics as covariates, ANCOVA test did not show any significant differences between groups.

Discussion

Introduction of physical activity into people's lives are valuable therapeutic interventions for NAFLD (6).

This study compared different intensities of aerobic exercise for the treatment of NAFLD. Although our results did not reach to statistical significant difference in the measured outcomes between the three arm of study, the before and after comparison revealed that moderate intensity exercise could have a beneficial role in reduction of serum aminotransferase. Also improvement in steatosis and fibrosis was observed in intervention group with high intensity aerobic exercise.

In this regard, Abdelbasset et al. (20) that compared the effect of High-Intensity Interval (HIIT) aerobic exercise with the moderate-intensity in diabetic patients with fatty liver, argue that the two exercise programs have similar effects on fatty liver.

Although there are significant changes in anthropometric and biochemistry outcomes in moderate intensity groups, the mean of steatosis and fibrosis did not reach to statistical significant difference. Similarly, a 2017 meta-analysis study conducted by Katsagoni et al, revealed that continuous high intensity exercise could be of more benefit to reduction the Intrahepatic TG (IHTG) than moderate and interval high intensity training (8).

The available evidence seems to point to reduction in the fat accumulation of the liver is independent of weight loss (21-28).

Table 2. Comparison of variables within groups. SE: Standard Error, CI: Confidence Interval, WHR: Waist Hip Ratio, FBS: Fasting Blood Sugar,TG: Triglycerides, HDL: High Density Lipoprotein, LDL: Low Density Lipoprotein, *: statistical significant.

Control (N=14)						Moderate intensity (N=13)					high intensity (N=13)				
	Paired difference				P	Paired difference				P	Paired difference				P
	Mean	SD	CI 95%			mean	SD	CI 95%			mean	SD	CI 95%		
			upper	lower				upper	lower				upper	lower	
Weight (kg)	1.76	3.27	3.65	-0.12	0.06	2.32	2.74	3.98	0.67	0.01*	1.53	2.25	2.96	0.09	.04*
BMI (kg/m2)	0.60	1.14	1.25	-0.06	0.07	0.86	1.00	1.47	0.26	0.01*	0.62	0.83	1.14	0.09	.03*
WC (CM)	1.21	6.21	4.80	-2.37	0.47	1.77	1.47	2.76	0.78	0.01*	1.31	1.75	2.37	0.25	0.02*
HC (CM)	1.28	5.09	4.22	-1.65	0.36	0.91	1.04	1.61	0.21	0.02*	0.15	1.99	1.36	-1.05	0.79
WHR	0.002	0.04	0.02	-0.02	0.85	0.01	0.01	0.01	0.00	0.01*	0.01	0.01	0.02	0.00	0.01*
PBF (%)	0.29	1.24	1.01	-0.42	0.39	0.05	2.71	1.68	-1.59	0.95	0.68	2.09	1.94	-.59	0.27
Fibrosis	-0.03	0.71	0.37	-0.44	0.85	0.57	1.54	1.49	-0.36	0.21	0.68	0.82	1.18	0.19	0.01*
Steatosis	19.42	31.42	37.57	1.28	0.03*	9.92	26.81	26.13	-6.28	0.21	14.62	18.03	25.51	3.72	0.01*
ALT (IU/L)	2.57	6.82	6.51	-1.36	0.18	8.23	10.07	14.31	2.15	0.01*	-0.46	15.64	8.99	-9.91	0.92
AST (IU/L)	0.00	5.09	2.94	-2.94	1.00	5.31	6.13	9.01	1.60	0.01*	-0.31	5.92	3.27	-3.89	0.85
Ferritin (ng/ml)	11.50	45.08	37.53	-14.53	0.35	-13.64	20.35	0.04	-27.31	0.05	27.92	51.29	58.92	-3.07	0.07
FBS (mg/dl)	-1.71	8.72	3.32	-6.74	0.47	15.27	28.52	34.43	-3.89	0.11	-0.46	5.91	3.11	-4.03	0.78
HbA1C	-0.05	0.60	0.29	-0.39	0.76	0.60	0.78	1.13	0.07	0.03*	0.02	0.75	0.47	-0.44	0.94
Insulin (mIU/L)	-0.58	1.42	0.23	-1.40	0.14	0.52	2.03	1.88	-0.84	0.42	-0.85	4.51	1.87	-3.58	0.51
TC (mg/dl)	-9.71	14.44	-1.37	-18.05	0.02*	10.45	33.51	32.96	-12.06	0.33	-0.62	17.20	9.78	-11.01	0.90
TG (mg/dl)	-10.5	12.30	-3.39	-17.60	0.01*	22.73	52.11	57.73	-12.28	0.18	0.31	37.01	22.68	-22.06	0.98
HDL (mg/dl)	-3.35	5.31	-0.28	-6.42	0.03*	1.82	8.94	7.83	-4.19	0.52	-0.54	5.64	2.87	-3.94	0.74
LDL (mg/dl)	-5.21	14.63	3.23	-13.66	0.20	5.91	16.14	16.75	-4.93	0.25	-6.92	11.91	0.27	-14.12	0.06
VO_2max ($ml/kg.min^{-1}$)	0.07	0.99	0.64	-0.50	0.79	-0.92	3.26	1.15	-2.99	0.35	-1.62	2.75	0.05	-3.28	0.06
FIB- 4	-0.06	0.21	0.05	-0.18	0.28	0.10	0.37	0.32	-0.12	0.33	-0.02	0.11	0.05	-0.08	0.61

Abbreviation

ALT: alanine aminotransferase, AST: aspartate aminotransferase, BMI: Body Mass Index, FBS: Fasting Blood Sugar, HC: Hip Circumference, HDL: High Density Lipoprotein, LDL: Low Density Lipoprotein, PBF: Percent of Body Fat, TC: Total Cholesterol, TG: Triglyceride, WC: Waist Circumference, WHR: Waist Hip Ratio * statistical significant.

Table 3. Comparison of variables between groups.

	Control (N=14)		Moderate (N=13)		High (N=13)		P value	
	Mean	SD	Mean	SD	Mean	SD	ANOVA	Factorial ANCOVA
Weight (kg)	80.71	13.23	81.94	19.18	79.40	16.48	.93	.61
BMI	31.22	6.10	30.56	5.71	29.12	4.55	0.62	0.63
WC (cm)	100.93	11.05	103.91	16.54	97.08	10.39	0.42	0.38
HC (cm)	107.36	9.07	110.36	16.66	103.62	6.84	0.35	0.14
WHR	0.94	0.07	0.80	0.36	0.94	0.06	0.63	0.38
PBF (%)	32.39	6.66	32.69	7.58	28.20	6.01	0.18	0.94
Fibrosis	6.53	2.08	7.48	2.14	6.95	2.16	0.51	0.44
Steatosis	289.86	40.08	296.77	32.96	293.85	38.15	0.89	0.87
ALT (IU/L)	44.21	16.58	28.15	16.42	47.77	25.09	0.03*	0.52
AST (IU/L)	31.57	13.17	21.62	8.13	33.69	21.06	0.10	0.64
Ferritin (ng/ml)	118.29	50.88	83.18	35.96	132.08	54.10	0.05	0.76
FBS (mg/dl)	104.50	17.81	103.00	10.44	96.54	10.65	0.30	0.32
HbA1c	6.00	1.14	5.50	0.85	5.28	0.76	0.14	0.17
Insulin (mIU/L)	13.09	4.36	15.63	10.39	12.85	6.24	0.59	0.29
TC (mg/dl)	172.07	34.61	175.64	51.39	171.08	20.53	0.95	0.61
TG (mg/dl)	212.00	69.55	156.91	80.03	210.38	103.70	0.22	0.54
HDL (mg/dl)	39.64	10.53	43.82	9.68	42.69	8.93	0.54	0.93
LDL (mg/dl)	104.21	21.90	108.00	43.52	98.46	13.16	0.70	0.74
VO_2max ($ml/kg.min^{-1}$)	26.71	5.00	25.92	5.90	34.15	6.64	0.002*	0.17
FIB- 4	1.64	0.65	1.47	0.41	1.54	0.66	0.75	0.32

Abbreviation

ALT: alanine aminotransferase, AST: aspartate aminotransferase, BMI: Body Mass Index, FBS: Fasting Blood Sugar, HC: Hip Circumference, HDL: High Density Lipoprotein, LDL: Low Density Lipoprotein, PBF: Percent of Body Fat, TC: Total Cholesterol, TG: Triglyceride, WC: Waist Circumference, WHR: Waist Hip Ratio * statistical significant.

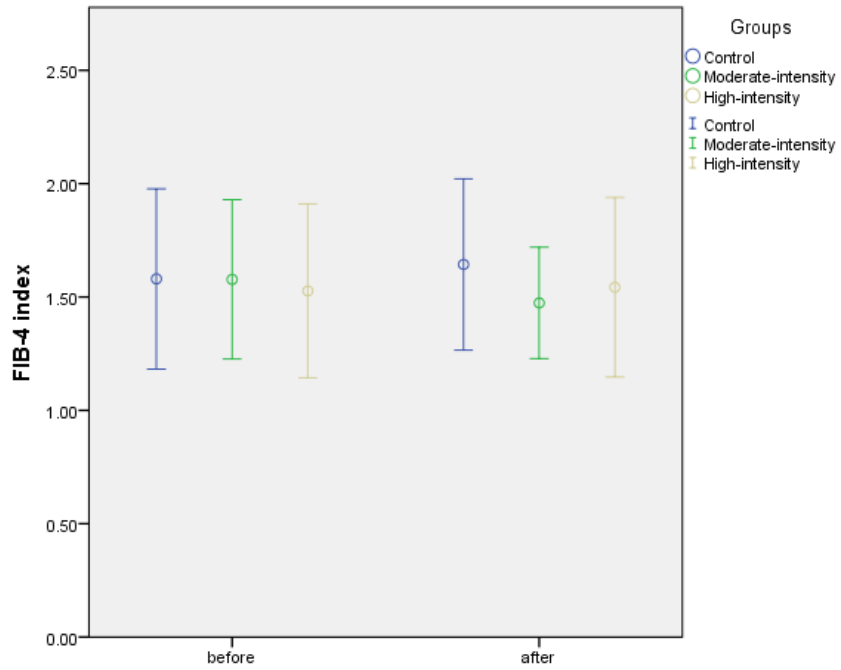

Figure 2. Changes in FIB-4 index between before and after intervention by treatment arm.

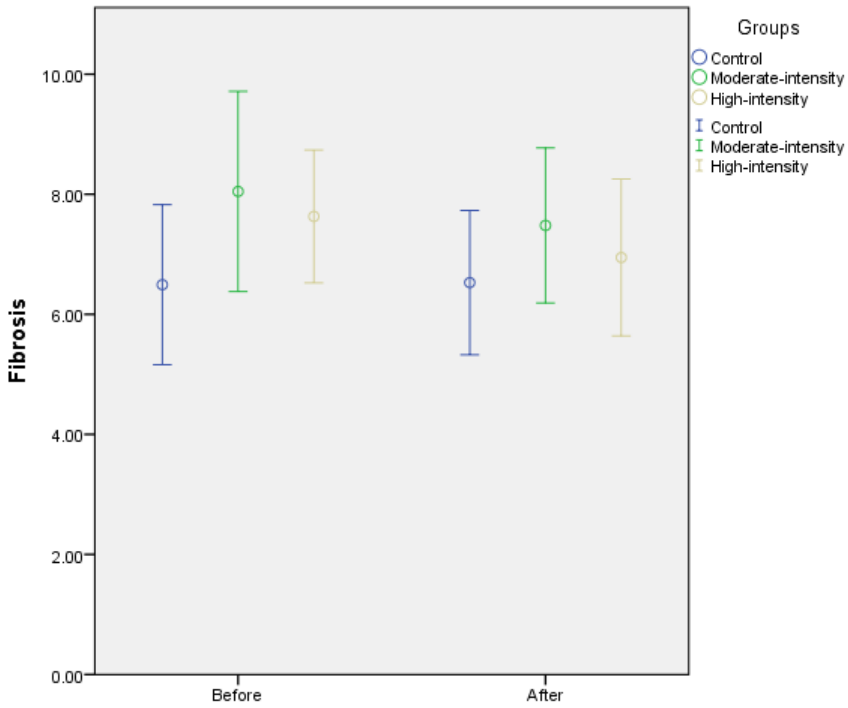

Figure 3. Changes in fibrosis between before and after intervention by treatment arm.

The results of this study also showed that aerobic exercise with independent of weight loss can reduce the rate of steatosis. Improvements in insulin resistance, fatty acid metabolism in the liver, the mitochondrial function of the liver, and inflammatory cascade activity appear to be molecular mechanisms for this effect (7).

Saldiran et al., who compared aerobic exercise for 8 weeks with and without vibration, reported a decrease in liver enzymes in their study groups (29). In the current study only in the group with moderate aerobic exercise, statistical analysis showed a significant difference in the reduction of liver enzymes. However,

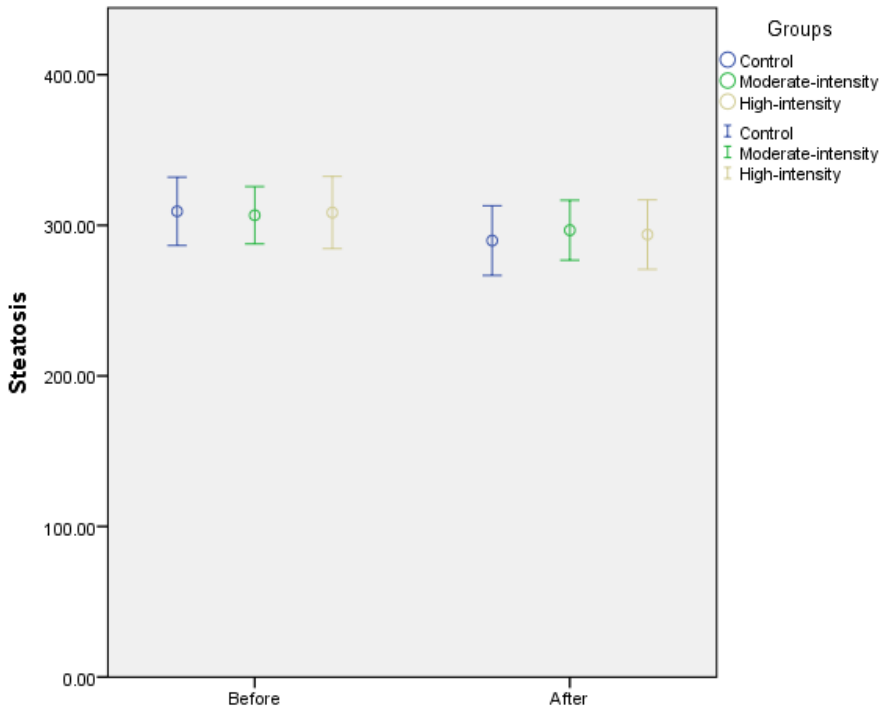

Figure 4. Changes in steatosis between before and after intervention by treatment arm.

the overall course of enzymes, especially ALT in all three groups was reduced. The relevant guidelines in this regard, despite the recommendation to study these enzymes for patients' follow-up, state that the reduction of liver fat content is not necessarily accompanied by a decrease in liver enzymes (29).

The present study showed that moderate-intensity aerobic exercise can effectively improve HBA1c levels in NAFLD patients, a finding not found in the group with high-intensity aerobic exercise. However, other insulin resistance factors, such as FBS and insulin levels, did not change significantly in any of the study groups. Along this line, previous studies mentioned that moderate-intensity exercise can play a more effective role in improving blood sugar levels than high-intensity exercise (30, 31).

Strength and Limitation

Since the follow-up period in this study was six months, it seems that this relatively long time has been able to show the changes caused by fibrosis in patients with fatty liver. However, this strength point leads to a relatively significant drop in participants. Although, the rate of loss was similar among participants in different study groups, high rate of drop out could lead to attrition bias.

Another strength point of this study was the supervision of intervention groups. Also the use of TE order to determine CAP score in this study could be a strong point.

In this study, we sought to determine the appropriate intensity of exercise therapy in NAFLD patients. Since, according to ethics, we could not exclude patients from exercise as an effective intervention for NAFLD, general recommendations for aerobic exercise were also given to the control group. Another limitation in this study was the non-withdrawal of NASH patients. It is likely that NASH is more prone to cirrhosis in comparison with simple steatosis (32). In light of these consideration, the therapeutic effect of exercise for NAFLD patients might underestimated in this study.

Conclusion

The present study suggests that both moderate and high intensity aerobic exercise can improve the course of disease in NAFLD patients. However, improvement in steatosis and fibrosis was more evident in high intensity training. Considering the high rate of drop out in the current study, caution is needed in interpretation of the results. Further large and well-designed RCTs are needed order to generalize the findings.

Acknowledgement

Special thanks to our clients in Tabriz children's hospital for their patience and cooperation in this study.

Conflict of interests

The authors declare that they have no competing interests.

References

1. Franco I, Bianco A, Mirizzi A, Campanella A, Bonfiglio C, Sorino P, et al. Physical activity and low glycemic index Mediterranean diet: Main and modification effects on NAFLD score. Results from a randomized clinical trial. Nutrients 2020;13:66.

2. Younossi Z, Anstee QM, Marietti M, Hardy T, Henry L, Eslam M, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol 2018;15:11-20.

3. De Minicis S, Day C, Svegliati-Baroni G. From NAFLD to NASH and HCC: pathogenetic mechanisms and therapeutic insights. Curr Pharm Des 2013;19:5239-5249.

4. Leoni S, Tovoli F, Napoli L, Serio I, Ferri S, Bolondi L. Current guidelines for the management of non-alcoholic fatty liver disease: a systematic review with comparative analysis. World J Gastroenterol 2018;24:3361.

5. Westfall E, Jeske R, Bader AR. Nonalcoholic fatty liver disease: common questions and answers on diagnosis and management. Am Fam Physician 2020;102:603-612.

6. Dong F, Zhang Y, Huang Y, Wang Y, Zhang G, Hu X, et al. Long-term lifestyle interventions in middle-aged and elderly men with nonalcoholic fatty liver disease: a randomized controlled trial. Sci Rep 2016;6:1-8.

7. van der Windt DJ, Sud V, Zhang H, Tsung A, Huang H. The effects of physical exercise on fatty liver disease. Gene Expr 2018;18:89.

8. Katsagoni CN, Georgoulis M, Papatheodoridis GV, Panagiotakos DB, Kontogianni MD. Effects of lifestyle interventions on clinical characteristics of patients with non-alcoholic fatty liver disease: a meta-analysis. Metabolism 2017;68:119-32.

9. Farzanegi P, Dana A, Ebrahimpoor Z, Asadi M, Azarbayjani MA. Mechanisms of beneficial effects of exercise training on non-alcoholic fatty liver disease (NAFLD): roles of oxidative stress and inflammation. Eur J Sport Sci 2019;19:994-1003.

10. Schwenzer NF, Springer F, Schraml C, Stefan N, Machann J, Schick F. Non-invasive assessment and quantification of liver steatosis by ultrasound, computed tomography and magnetic resonance. J Hepatol 2009;51:433-445.

11. Talwalkar JA, Kurtz DM, Schoenleber SJ, West CP, Montori VM. Ultrasound-based transient elastography for the detection of hepatic fibrosis: systematic review and meta-analysis. Clin Gastroenterol Hepatol 2007;5:1214-1220.

12. Malekzadeh R, Poustchi H. Fibroscan for assessing liver fibrosis: an acceptable alternative for liver biopsy: fibroscan: an acceptable alternative for liver biopsy. Hepat Mon 2011;11:157.

13. Shah AG, Lydecker A, Murray K, Tetri BN, Contos MJ, Sanyal AJ, et al. Comparison of noninvasive markers of fibrosis in patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2009;7:1104-1112.

14. Ferraioli G, Tinelli C, De Silvestri A, Lissandrin R, Above E, Dellafiore C, et al. The clinical value of controlled attenuation parameter for the noninvasive assessment of liver steatosis. Liver Int 2016;36:1860-1866.

15. Khalil SF, Mohktar MS, Ibrahim F. The theory and fundamentals of bioimpedance analysis in clinical status monitoring and diagnosis of diseases. Sensors 2014;14:10895-10928.

16. de Lédinghen V, Vergniol J, Foucher J, Merrouche W, le Bail B. Non-invasive diagnosis of liver steatosis using controlled attenuation parameter (CAP) and transient elastography. Liver Int 2012;32:911-918.

17. Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology 2006;43:1317-1325.

18. ACoS M. ACSM's guidelines for exercise testing and prescription. Lippincott Williams & Wilkins Philadelphia; 2013.

19. DeSimone GT. The Tortoise Factor—Get FITT. ACSM's Health Fit J 2019;23:3-4.

20. Abdelbasset WK, Tantawy SA, Kamel DM, Alqahtani BA, Elnegamy TE, Soliman GS, et al. Effects of high-intensity interval and moderate-intensity continuous aerobic exercise on diabetic obese patients with nonalcoholic fatty liver disease: a comparative randomized controlled trial. Medicine 2020;99.

21. Hallsworth K, Fattakhova G, Hollingsworth KG, Thoma C, Moore S, Taylor R, et al. Resistance exercise reduces liver fat and its mediators in non-alcoholic fatty liver disease independent of weight loss. Gut 2011;60:1278-1283.

22. Golabi P, Locklear CT, Austin P, Afdhal S, Byrns M, Gerber L, et al. Effectiveness of exercise in hepatic fat mobilization in non-alcoholic fatty liver disease: Systematic review. World J Gastroenterol 2016;22:6318.

23. Eckard C, Cole R, Lockwood J, Torres DM, Williams CD, Shaw JC, et al. Prospective histopathologic evaluation of lifestyle modification in nonalcoholic fatty liver disease: a randomized trial. Therap Adv Gastroenterol 2013;6:249-59.

24. Bacchi E, Negri C, Targher G, Faccioli N, Lanza M, Zoppini G, et al. Both resistance training and aerobic training reduce hepatic fat content in type 2 diabetic subjects with nonalcoholic fatty liver disease (the RAED2 Randomized Trial). Hepatology 2013;58:1287-1295.

25. Sumida Y, Nakajima A, Itoh Y. Limitations of liver biopsy and non-invasive diagnostic tests for the diagnosis of nonalcoholic fatty liver disease/nonalcoholic steatohepatitis. World J Gastroenterol 2014;20:475.

26. Promrat K, Kleiner DE, Niemeier HM, Jackvony E, Kearns M, Wands JR, et al. Randomized controlled trial testing the effects of weight loss on nonalcoholic steatohepatitis. Hepatology 2010;51:121-129.

27. Keating SE, Hackett DA, Parker HM, Way KL, O'Connor HT, Sainsbury A, et al. Effect of resistance training on liver fat and

visceral adiposity in adults with obesity: A randomized controlled trial. Hepatol Res 2017;47:622-631.

28. Keating SE, Hackett DA, Parker HM, O'Connor HT, Gerofi JA, Sainsbury A, et al. Effect of aerobic exercise training dose on liver fat and visceral adiposity. J Hepatol 2015;63:174-182.

29. Saldiran TÇ, Mutluay FK, Yağci İ, Yilmaz Y, editors. Impact of aerobic training with and without whole-body vibration training on metabolic features and quality of life in non-alcoholic fatty liver disease patients. Ann Endocrinol (Paris) 2020: 81:493-499.

30. Slentz CA, Tanner CJ, Bateman LA, Durheim MT, Huffman KM, Houmard JA, et al. Effects of exercise training intensity on pancreatic β-cell function. Diabetes Care 2009;32:1807-1811.

31. Houmard JA, Tanner CJ, Slentz CA, Duscha BD, McCartney JS, Kraus WE. Effect of the volume and intensity of exercise training on insulin sensitivity. J Appl Physiol 2004;96:101-106.

32. Ong JP, Younossi ZM. Epidemiology and natural history of NAFLD and NASH. Clin Liver Dis 2007;11:1-16.