

Original Article





Aerobic exercise combined with whole body vibration in nonalcoholic fatty liver disease: A randomized controlled trial

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Abstract

Introduction: A whole-body vibration device (WBV) as an exercise option may be suitable for nonalcoholic fatty liver disease (NAFLD). This study aimed to compare the effects of combined aerobic exercise with WBV training and aerobic exercise alone on the liver enzymes and lipid profiles in NAFLD.

Methods: This randomized clinical trial was conducted on 32 patients with grade 1 and 2 NAFLD diagnosed by ultrasound. Patients were randomly divided into intervention and control groups. Patients in the intervention group were subjected to WBV with a frequency of 35-50 Hz before starting aerobic exercise. Wherein, aerobic exercises were performed using a treadmill at 60%-80% of maximum heart rate. Each session included a 5-minute warm-up, 30 minutes of treadmill, and 5 minutes of cooling at the end. Subjects in the control group underwent the same protocol but did not undergo WBV. Sessions were performed three times per week. The intervention lasted for eight weeks for both groups. Liver enzymes (alkaline phosphatase [ALP], alanine aminotransferase [ALT], aspartate aminotransferase [AST]), and lipid profiles (high-density lipoprotein [HDL], low-density lipoprotein [LDL], triglyceride, and cholesterol) were measured during a week before the exercises and after the trial.

Results: Mean serum ALT levels (45.5 vs. 31.5; P=0.003) and triglycerides (226.7 vs. 209.3; P=0.004) levels significantly decreased in the intervention group after the intervention. Although all liver enzymes and lipid profiles serum levels except for LDL decreased significantly in both groups (P<0.05), AST, ALP, cholesterol, LDL, and HDL levels showed no significant differences between the two groups.

Conclusion: The present study revealed that aerobic exercises with WBV significantly reduced ALT and triglyceride levels compared to aerobic exercises alone. In conclusion, the combined method can be recommended as a more effective method for patients suffering from NAFLD.

Introduction

Nonalcoholic fatty liver disease (NAFLD) is a complex liver disease that follows a progressive course, with various stages from the initial accumulation of fat in the liver to the development of nonalcoholic steatohepatitis, ultimately leading to liver cirrhosis and hepatocellular carcinoma.¹ The etiology of NAFLD remains poorly understood, with estimated differences observed among individuals. Nevertheless, the "multiple-hit hypothesis" serves as a valuable framework to enhance our comprehension of this condition. The initial occurrence of hepatic steatosis can be regarded as the "first hit", while subsequent or concurrent combinations of genetic predispositions, metabolic dysfunction (mainly insulin resistance), lifestyle factors, dietary patterns, and/or changes in the gut microbiome are all potential factors that may contribute to the progression of more severe liver disorders.² The activation of hepatic stellate cells and Kupffer cells is facilitated by the sequential or simultaneous activation of the adaptive and innate immune systems, leading to the progression of fibrosis and cirrhosis.^{3,4} Oftentimes, elevated transaminases are discovered during routine laboratory tests or when evaluating other disorders such as hypertension, hyperlipidemia, obesity, and diabetes.⁵ Elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are the most common laboratory abnormality. There is rarely an elevation exceeding 2 to 3 times the upper limits of normal.⁶ The diagnosis of NAFLD is subject to several criteria. There must be no history of significant alcohol use among the patients under consideration. The management of glucolipid metabolism remains a primary focus in the treatment of NAFLD. Furthermore, there has been an increase in research efforts focused on the manipulation of the gut

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microbiota as a potential approach for the treatment of NAFLD. Pharmaceutical interventions have not been successful in treating NAFLD, and researchers are currently developing various medications that are undergoing clinical trials.⁷ Therefore, lifestyle intervention involving dietary changes and structured exercise is the mainstay of treatment.8 Developing NAFLD is arguably influenced most by weight gain, whereas weight loss leads to decreased liver fat and aminotransferase levels. It has been established that physical exercise is beneficial for managing NAFLD.9 However, it may be difficult for some people to maintain exercise in daily life without assistance. Patients who have difficulty engaging in exercise may benefit from whole-body vibration device (WBV) as an exercise modality.¹⁰ Unlike pharmacotherapies, exercise is the foundation of NAFLD management.¹¹ A variety of health consequences are improved in patients with NAFLD through both aerobic and resistance exercise. Nevertheless, WBV is a novel alternative that has recently been introduced. By generating intense stimulation passively, this exercise changes the length of muscle fibers dynamically.¹⁰ During the procedure, patients are exposed to rapid and repeated oscillations via a vibration device. With brief exposure to vibration, this form of exercise stimulates muscles strongly. In various fields of medicine and physiology, WBV has been found to be effective. WBV induces physiological improvements in human subjects, impacting their neuromuscular, respiratory, and cardiovascular functions.12 The beneficial effects of this treatment have been studied and confirmed in various conditions, such as osteoporosis, fractures, and metabolic syndrome.¹³⁻¹⁵ Because of its effectiveness and ease of use, WBV is a suitable exercise method for patients who have difficulty engaging in general exercise.^{16,17} The interest in the WBV intervention arises from the fact that it requires minimal energy and motivation from the practitioner. In addition, it needs a minimal duration of exposure (approximately 5-15 minutes per session), rendering it an attractive alternative when the performance of normal physical exercises is impossible.^{18,19} The current study evaluated whether WBV in combination with aerobic exercise could reduce lipid profiles and liver enzymes more effectively than aerobic exercise alone in patients with NAFLD.

Materials and Methods

Study design and setting

This randomized clinical trial was conducted on 32 patients aged 27-62 years with grade 1 and 2 NAFLD diagnosed by ultrasound and referred to Imam Reza hospital in Tabriz. The process of participant recruitment up to the conclusion of the intervention lasted for a period of 18 months. Before starting the study, informed consent was obtained from all participants. The inclusion criteria were grade 1 and 2 NAFLD diagnosed by ultrasound and BMI between 27-35, the exclusion criteria were

2 | J Res Clin Med, 2024, 12: 39

consumption of alcohol exceeding five units per week, the use of hepatotoxic drugs such as amiodarone, tamoxifen, methotrexate, fibrate, etc., and exercise contraindications such as cardiopulmonary or musculoskeletal conditions, including severe knee arthritis.

Randomization and intervention

Participants were randomly assigned to intervention groups (16 subjects) and control groups (16 subjects). Wherein, block randomization with fixed size was used for randomization. Because of the study type, it was not possible to blind therapists and patients but blinding was used during evaluation and analysis. In the convenience method, gastroenterologists introduced sampling samples as a series and then entered them into the study. A gastroenterologist diagnosed patients with NAFLD grade 1 or 2, and based on inclusion criteria, patients were included in this study. Patients in the intervention group were subjected to WBV (Azimuth standing massager and vibrator model AZ 904-1) with a frequency of 35-50 Hz before starting aerobic exercise. Wherein, aerobic exercises were performed using a treadmill at 60%-8% of maximum heart rate. Hence, each session included a 5-minute warm-up, 30 minutes of treadmill, and 5 minutes of cooling at the end. Subjects in the control group underwent the same protocol but did not undergo WBV. Sessions were performed 3 times per week. The intervention for both groups lasted for eight weeks. All interventions in two groups were conducted with the presence and supervision of the researcher, and therefore, except for two cases of sample loss, all participants had full participation in the entire procedure. In both groups, liver enzymes (alkaline phosphatase [ALP], ALT, AST) and lipid profiles (high-density lipoprotein [HDL], lowdensity lipoprotein [LDL], triglyceride, and cholesterol) were measured during a week before the exercises and after the trial. It was advised to all participants to continue their drug treatments and diet regimen during the study.

Sample size

We calculated the sample size based on the study of Khaoshbaten et al²⁰ using G*Power software and taking into account m1 = 176, sd1 = 5.2 (the mean serum triglyceride after aerobic exercise) and m2 = 158.4, sd2 = sd1 = 5.2 (the mean serum triglyceride with an assumption of 10% decrement following adding WBV) α = 0.05, power = 80%, and two-sided test equal to 5 people in each group. Also, considering m1 = 43.5, sd1 = 2.4 (the mean serum ALT after aerobic exercise) and m2 = 39.15, sd2 = sd1 = 2.4 (the mean serum ALT with the assumption of 10% decrement following adding WBV), α = 0.05, power = 80%, and two-sided test equal to 15 people in each group. Finally, after considering the 10% possible dropout, 16 people for each group and a total of 32 people were estimated.

Statistical Analysis

In this study, before using statistical tests and making

inferences based on the data, the distributions of cholesterol, triglyceride, AST, ALT, HDL, LDL, and ALP were evaluated before and after aerobic exercise by using the Kolmogorov-Smirnov test. To compare baseline variables, an independent t-test and Fisher's exact test were used. Comparing before and after was performed using paired t-test and Wilcoxon, and laboratory values were compared using ANCOVA adjusted for baseline and Mann-Whitney. Depending on the type of hypothesis, appropriate statistical tests were performed and interpreted as one-tailed. All analysis was done using Stata analyses, and a *p*-value less than 0.05 was considered significant.

Results

The quantitative variables included in the current study were age, cholesterol, triglycerides, AST, ALT, HDL, LDL, and ALP. ALT and AST variables had non-normal distributions because of *P* values less than 0.05. Except for age, all of the variables were measured one week before and after the intervention. A total of 32 subjects participated in the study. Subjects were randomly assigned to the intervention group (16 subjects) and the control group (16 subjects). Within two weeks, one patient from each group was removed and 15 patients remained. The remaining 30 patients were 11 men (37%) and 19 women (63%) in total (Figure 1).

In the control group, the average age was 41.35, while in the intervention group, it was 44.56 (P=0.36). There were no significant differences between-groups in terms of BMI and gender (Table 1).

Liver enzyme levels in response to aerobic exercise with and without WBV

The mean ALT levels decreased significantly after aerobic exercises with and without vibration compared to baseline (P<0.05). The difference between the two groups was significant (P=0.003), indicating that aerobic exercise with vibration significantly decreased ALT in comparison with the control group (Table 2).

The mean AST levels significantly decreased within both groups compared to baseline (p-value < 0.05). However, no significant between groups difference was observed following the intervention (P=0.090; Table 2).

Both aerobic exercises with vibration and aerobic exercise alone reduced the mean serum ALP (P < 0.05). The comparison of ALP levels showed no significant difference between the intervention and control groups (P = 0.064; Table 2).

Lipid profile levels in response to aerobic exercise with and without WBV

The mean cholesterol levels significantly decreased within both groups compared to baseline (P < 0.05). However, no significant difference between groups was observed following intervention (P = 0.519; Table 2).

The mean triglyceride levels in aerobic exercises with vibration and aerobic exercise alone significantly decreased compared to baseline (P < 0.05). On the other hand, the comparison of triglyceride levels between the intervention and control groups displayed a significant difference (P = 0.04; Table 2).

In both the intervention and control groups, the mean LDL levels before and after aerobic exercise were not significantly different from baseline. However, no significant between groups difference was observed following intervention (P=0.436; Table 2).

In both groups, aerobic exercises (whether vibrating or not vibrating) significantly decreased HDL levels compared to baseline (P < 0.05) in patients with NAFLD. Meanwhile, the comparison of HDL levels between the intervention and control groups displayed no significant difference (P = 0.829; Table 2).

Discussion

This study showed that WBV coupled with aerobic exercise reduced liver enzymes and fat levels in patients with NAFLD. Among 32 patients with fatty liver, patients undergoing WBV and aerobic exercise had lower levels of ALT and triglycerides than patients who performed aerobic exercise alone. However, it did not show any additional effect on LDL, cholesterol, HDL, AST, and ALP, although according to the findings of this study, in both groups, the levels of HDL, ALT, AST ALP, cholesterol, and triglycerides decreased significantly, but the level of LDL in neither group was reduced.

NAFLD is a multifaceted condition connected to diverse metabolic risk factors and increases the risk of mortality associated with hepatic and cardiovascular conditions. With the increase in life expectancy, NAFLD has emerged as a significant global health challenge. It has been well established that physical exercise is beneficial for managing NAFLD.21 A progressive loss of muscle mass and strength (sarcopenia) in older people, decreases the quality of life, increases the possibility of disability, and contributes to higher body fat, raising the risk of type 2 diabetes. Keeping active and participating in regular sports activities can delay the aging process, but there are risks associated with injuries and reduced mobility for the elderly.²² WBV is a safe method and can be used for a long time as a passive exercise modality, and it can directly increase energy consumption and thus cause weight loss, as evidenced in several studies. When combined with other treatment methods, such as diet restrictions or resistance exercises, this method can cause weight loss as well. Compared to young people, WBV may have more beneficial effects on elderly people, and it can cause further improvements in health and quality of life.23 According to the previous study that was conducted on the effect of aerobic exercise on NAFLD,²⁴ short-term aerobic exercise increases the unsaturated fat indices, and similar results were observed in our study. However,

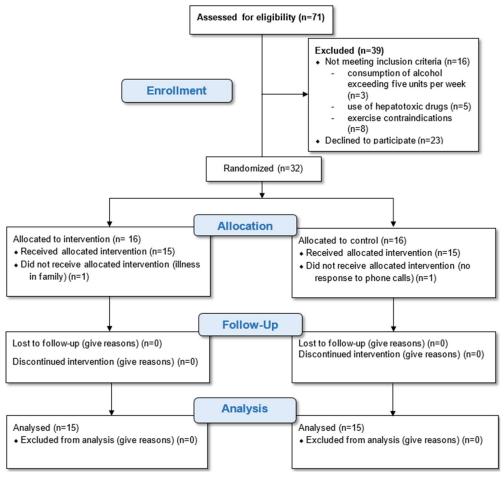


Figure 1. The consort flowchart of study

 Table 1. Baseline characteristics of the participants

Variables		Intervention	Control	P value	
NAFLD, No. (%)	Grade I	10 (62.5)	7 (43.7)	0.479ª	
1 Λ 1 D , 1 0 . (70)	Grade II	6 (37.5)	9 (56.3)	0.479	
Gender, No. (%)	Male	6 (37.5)	5 (31.2)	0.922ª	
Gender, No. (%)	Female	10 (62.5)	11(68.8)		
Age (y), Mean \pm SD		44.56 ± 12.2	41.35 ± 13.5	0.362 ^b	
Body mass index (kg/m Mean±SD	²),	28.8 ± 1.5	29.3 ± 1.9	0.536 ^b	

NAFLD: Non-alcoholic fatty liver disease, SD: Standard deviation.

^a Fisher exact test; ^b Independent t-test.

the mentioned study found that aerobic exercise did not reduce triglyceride levels, whereas our study found that aerobic exercise also reduced triglyceride levels, most likely because the duration of exercise in our study was longer, and it appears that long-term aerobic exercise for at least eight weeks has a positive effect on triglycerides. According to another study in South Korea on the effects of regular aerobic exercise on non-alcoholic fatty liver patients,²⁵ the patients were at reduced risk of developing NAFLD if these regular aerobic exercises were performed three times a week for a minimum of 30 minutes a day for more than three months. Additionally, it improves the metabolism of liver fat and liver enzymes, which we

4 | J Res Clin Med, 2024, 12: 39

have also observed in our study to decrease fat and liver enzymes. Similarly, other studies have also reported a decrease in liver enzymes in non-alcoholic fatty liver patients following exercise.²⁰ According to another study, WBV reduced visceral fat and liver triglyceride content in old rats in an animal study.23 Furthermore, the content of liver fat (9.9%) and visceral fat (6.2%) decreased significantly in alcoholic fatty liver patients following WBV therapy over 6 months in human samples.¹⁰ According to the results of this study, WBV combined with regular exercise reduces blood triglyceride levels and regulates liver enzymes more effectively. Many types of aerobic exercise may be difficult or impossible for the elderly, especially those with musculoskeletal problems and limitations. WBV appears to improve lipid profile and reduce liver enzymes in these people when used as an auxiliary treatment method. Additionally, in several studies that have been conducted on the effects of the vibration method on the whole body, muscle mass, and bone density have also increased.²⁶ These cases suggest that this method is very helpful, particularly for the elderly.

Conclusion

Our study compared the effect of aerobic exercises with

Table 2. The comparison of basic information description before and after trial

Variable	Intervention		0 .1 .3	Control		D .1 .3	n I h
	Pre-test	Post-test	- P value ^a	Pre-test	Post-test	P value ^a	<i>P</i> value ^b
ALP	133.0±31.5	113.2±22.3	< 0.001	135.0±33.6	123.5±16.1	< 0.001	0.064
ALT	47.3 ± 21.3	31.5 ± 15.1	< 0.001	49.3 ± 19.5	45.5 ± 19.8	0.032	0.003 ^c
AST	48.4 ± 18.7	35.7±13.7	< 0.001	48.8 ± 16.8	41.5 ± 14.6	0.014	0.090 ^c
Cholesterol	234.9 ± 28.6	220.4 ± 22.4	< 0.001	236.8±31.6	225.8 ± 25.6	0.005	0.519
Triglyceride	243.7 ± 33.4	209.3 ± 18.3	< 0.001	239.2 ± 37.5	226.7 ± 24.2	0.018	0.040
LDL	117.4 ± 17.9	112.5 ± 15.4	0.122	121.4 ± 17.9	116 ± 21.2	0.104	0.430
HDL	36.0 ± 5.5	39.7 ± 5.8	0.044	37.0 ± 5.5	40.1 ± 6.6	0.046	0.529

Abbreviations: ALT, alanine aminotransferase; AST, Aspartate aminotransferase; ALP, alkaline phosphatase; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Note: Total data are expressed as mean \pm SD, with P values indicating statistical significance (P<0.05) presented in bold.

^a Paired t-test; ^b ANCOA adjusted for baseline values; ^c Mann-Whitney test.

and without vibration on non-alcoholic fatty liver patients. We concluded from our analysis that in non-alcoholic fatty liver patients, aerobic exercise with or without vibration reduces ALT, AST, ALP, cholesterol, and triglycerides, but does not affect LDL levels significantly. While the level of HDL in non-alcoholic fatty liver patients increases as a result of these therapies. We also revealed that vibration along with aerobic exercise reduces the levels of ALT and triglycerides in patients with NAFLD, but did not significantly influence the levels of AST, ALP, LDL, and HDL cholesterol in non-alcoholic fatty liver patients. Thus, this approach can be beneficial to patients with NAFLD who have musculoskeletal diseases or are unable to perform physical activities because of age or disability.

Limitations and suggestions of the study

The study faced limitations due to a small sample size, highlighting the requirement for a larger sample size in subsequent research. Moreover, in this study WBV was applied in conjunction with aerobic exercise, so the effects of vibration alone cannot be extracted. Thus, it is recommended that future investigations explore the effects of WBV without any additional exercise. After the intervention, biochemical tests were used to evaluate serum levels of liver enzymes and lipid profiles. Ultrasound was not used for further examination. This method is recommended for future research. The present study also faced limitation because did not consider data on insulin resistance, particularly HOMA-IR. This examination is also suggested in upcoming research. Furthermore, it is recommended in light of the beneficial effect of this method in old animal samples as compared to young animals, that future studies compare the effectiveness of this method between young and old individuals. Furthermore, we did not investigate the baseline physical activity and didn't measure the weight of participants after intervention.

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Study Highlights

What is current knowledge?

• Aerobic exercise as a suitable option has advantages in non-alcoholic fatty liver disease.

What is new here?

• Combined aerobic exercise with whole-body has further positive effects compared to aerobic exercise alone in NAFLD.

Authors' Contribution

Conceptualization: Yaghoub Salekzamani. Data curation: Soraya Babaie. Formal analysis: Azizeh Farshbaf-Khalili. Investigation: Azizeh Farshbaf-Khalili. Methodology: Yaghoub Salekzamani. Supervision: Manouchehr Khoshbaten. Writing–original draft: Soraya Babaie. Writing–review & editing: Manouchehr Khoshbaten.

Competing Interests

The authors declare that there is no conflict of interest.

Ethical Approval

This study was approved by the Ethics Committee of Tabriz University of Medical Sciences (IR. TBZMED.REC.1394.37) and registered on the website of the Iranian Clinical Trial Registry (identifier: IRCT201604162664N3, https://trialsearch.who. int/Trial2.aspx?TrialID=IRCT201604162664N3 . This study meticulously observed ethical considerations under the Helsinki Declaration. The protocol has been revised by the appropriate institutional review body.

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