Comparing the effectiveness of nutritional education with and without physical activity on blood lipids and liver aminotransferase enzymes in men with non-alcoholic fatty liver disease

Abstract

Aims: Fatty liver disease is a type of fat accumulation in the liver parenchyma that can be related to lifestyle. Therefore, this study was conducted with the aim of comparing the effectiveness of nutrition education with and without physical activity on blood lipids and liver aminotransferase enzymes in men with non-alcoholic fatty liver disease.

Methods: This study is a randomized clinical trial with a control group. which was carried out on 80 employees working in South Pars gas complex in Jam in Iran suffering from fatty liver. The participants were allocated to four nutrition education groups (alone), physical activity group (alone), nutrition education group with physical activity, and control group (20 people each) using random block sampling method. In all four groups, 48 hours before the intervention, 3 and 6 months after the intervention, blood lipids and liver enzymes were measured and recorded in a form. Data were analyzed using SPSS software (version 21) and chi-score statistics, one-way ANOVA and repeated measures ANOVA test. The significance level was $p<0.05$.

Findings: The average age of the participants was 38.7±4.7 years. Alanine aminotransferase enzyme showed a significant improvement in each of the 3 intervention groups of physical activity, nutrition education and combined compared to the control group at 3 and 6 months after the research intervention (P=0.001). Low-density lipoprotein showed a significant improvement in 6 months, and this difference was related to the group of physical activity combined with nutrition education (P=0.005).

Conclusion: Considering the greater effectiveness of exercise and diet intervention in a longer period of time, the use of this intervention in the long term for the prevention and treatment of non-alcoholic fatty liver disease is recommended to health officials and personnel.

Key words: non-alcoholic fatty liver, diet, physical activity, education, lipoprotein, alanine aminotransferase

Introduction

Non-alcoholic fatty liver disease (NAFLD) is characterized by the accumulation of fat in the liver, with more than 5% of the liver's total weight being fat [1]. The prevalence of NAFLD worldwide ranges from 8 to 45% [2]. In Iran, the prevalence of mild, moderate, and severe fatty liver disease is estimated at 26.7%, 7.6%, and 0.5%, respectively [3]. This disease is a systemic disorder with a multifactorial and complex pathogenesis [3-5]. Decreased physical activity and unhealthy diet in Asian countries have led to a 25% increase in obesity and the prevalence of this disease [6]. The main risk factors for this disease include obesity, insulin resistance, and dyslipidemia [7]. NAFLD, coupled with the obesity epidemic, is estimated to be one of the leading causes of liver-related morbidity and mortality by 2030 [8]. NAFLD can manifest from asymptomatic to fatigue, dyspepsia, right upper quadrant pain, and hepatosplenomegaly and is associated with age, gender, ethnicity, and endocrine disorders [8] as well as metabolic disorders, cardiovascular disease [9], chronic kidney disease, sleep apnea, obesity, insulin resistance, and diabetes [10].

With an increase in hepatic triglyceride concentrations, the lipid profile in patients with NAFL is affected, characterized by a reduction in HDL and an increase in LDL [11]. Elevated levels of liver enzymes such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) are features of NAFL disease [12]. Therapeutic interventions for fatty liver disease may include insulin sensitizers and incretions, lipid-lowering medications (such as statins), antioxidants including vitamin E, and treatment for vitamin D3 deficiency [13]. Drug therapies have not always been successful in reducing steatosis or liver inflammation or have undesirable side effects such as weight gain [1, 14]; hence, no drug or surgical method has been approved for NAFL treatment [17]. Therefore, early diagnosis and intervention, as well as prevention of complications, are proposed as optimal strategies for managing NAFL. Lifestyle modification including dietary interventions and exercise remains the primary treatment method for patients with this disease [15]. Treatment focuses on lifestyle modifications such as physical activity and adopting healthy eating habits because body weight and metabolic risk factors associated with metabolic syndrome are controlled [2]. Exercise helps reduce visceral fat mass, increase lipolysis, decrease release of pro-inflammatory cytokines, and create an anti-inflammatory environment, all of which play a role in controlling NAFL [16]. While exercise has advantages in improving insulin sensitivity and reducing body mass index, dietary interventions may be more effective in improving aminotransferase levels [7].

Excessive consumption of food, diets rich in fats or carbohydrates, can reduce insulin sensitivity and lead to non-alcoholic fatty liver disease by increasing serum free fatty acid levels [17]. Some dietary pattern rich in whole grains, legumes, fruits, vegetables, and dairy products plays a fundamental role in this effectiveness. Whole grains have lower glycemic index and higher fiber content. Calcium content in dairy products contributes to reducing visceral fat. Increased consumption of fruits and vegetables is associated with reduced risk of hypertension, type 2 diabetes, and increased satiety, aiding in weight loss. Conversely, consuming high-energy foods such as high-fat or refined carbohydrate foods can lead to excess calorie intake, resulting in obesity, overweight, and chronic diseases including fatty liver disease [18].

In the study by Kastagoni *et al.* (2017), exercise alone or combined with dietary intervention resulted in improved serum levels of liver enzymes and liver fat [19]. Gelli *et al.* (2017) demonstrated that a Mediterranean diet and a more active lifestyle could be a safe therapeutic approach for reducing the severity of NAFL and related diseases [1]. In the study by Hosseini kakhk *et al.* (2014), eight weeks of combined aerobic-resistance training along with nutrition or nutrition alone did not significantly affect serum aminotransferases [20]. Shamsaldini *et al.* also found in a study that aerobic and resistance exercises alone could reduce the levels of liver enzymes in patients with non-alcoholic fatty liver disease [12].

Given the significant role of lifestyle interventions in NAFL and the conflicting results of the aforementioned studies, there is a need for more precise evidence regarding the effects of exercise and diet on this disease. Therefore, the present study aimed to compare the effectiveness of six-month interventions of nutrition education with and without physical activity on blood lipids and liver aminotransferase enzymes in men with non-alcoholic fatty liver disease.

Instrument & Methods

Experimental design

This study is a pre-post clinical trial with a control group, registered under code N120180425039409IRCT on the Iranian Clinical Trials Registry website. The study was conducted from December 2018 to July 2019.

Participants, sampling, sample size calculation, and settings

Participants in the study were employees working in the South Pars Gas Complex in Jam, Iran, diagnosed with non-alcoholic fatty liver disease.

The sample size was calculated using tables based on the Cohen formula, considering an effect size of 0.4 and a test power of 80%. For the analysis of variance of four groups, the required sample size was determined to be 16 individuals per group. In addition, considering the sample size in most similar studies [21, 22] as 17 individuals and accounting for a 20% dropout rate, 20 individuals per group were selected, totaling 80 individuals overall.

The participants were selected using non-probability convenience sampling, but they were allocated to the four groups (nutrition education alone, physical activity alone, combined nutrition education and physical activity, and control group) using block randomization method with equal sizes. Inclusion criteria for the study included being male, aged at least 20 years, and confirmation of non-alcoholic fatty liver disease diagnosis in the sonography report by a specialist physician (grade 2 non-alcoholic fatty liver disease). Exclusion criteria for the study included receiving nutritional education intervention and regular exercise program in the past year, alcohol and drug consumption, metabolic diseases, endocrine disorders, liver diseases such as viral hepatitis B and C, hypothyroidism, undergoing surgery for weight loss due to reasons other than the intervention.

Interventions

Group 1: Nutrition Education Intervention: In this group, patients received education on healthy dietary patterns and nutrition for non-alcoholic fatty liver disease (NAFLD) by a nutritionist in the presence of the researcher. The education method involved group discussions and lectures, and educational materials were provided to the participants in the form of booklets. Additionally, in the present study, participants were visited by a nutritionist every two weeks (a total of 12 sessions), and during each visit, the nutritionist emphasized the adherence to the educational points by the patients. The educational booklet included guidance on preventive and therapeutic nutrition for NAFLD, such as recognizing and recommending adherence to a healthy dietary pyramid, daily food group consumption patterns, recommended dietary regimens for reducing calorie intake, and dietary restrictions and limitations.

Group 2: Physical Activity Intervention: Intervention in this group was conducted through practical demonstration and group lectures, showing the skills and types of physical activity. In each session, to ensure proper exercise performance, the researcher accompanied the participants. All participants were trained by an exercise physiology specialist and were under the control of the researcher for six months. The endurance exercise program was based on the recommendations of the American College of Sports Medicine. According to this protocol, aerobic exercise (brisk walking) was performed for 25 weeks, three sessions per week, and each session lasted for 40 minutes (5 minutes for warm-up and 5 minutes for cool-down), resulting in a total of 12 weeks of readiness and preparation. In this way, from the first week of brisk walking exercise on flat ground and in a designated path determined by the exercise physiology specialist and the researcher in Jam County, each session started with 10 minutes of brisk walking at 50% of maximum heart rate and three minutes were added to the duration each week until the end of the twelfth week. From the end of the twelfth week to the twenty-fifth week, the brisk walking program continued steadily (50 minutes). The desired heart rate (exercise intensity) during the 40-minute aerobic exercise was monitored by the individual during the exercise session.

In this study, considering the age of the participants and their non-athlete status, the exercise intensity of 50 to 75 percent of the maximum heart rate was calculated individually for each person according to the formula (maximum heart rate= age-220) [23].

Group 3: Nutrition and Physical Activity Education: In this group, participants received counseling on nutrition and interventions for physical activity. This means that individuals in this group received both types of interventions from groups 1 and 2.

Group 4: Control Group: Participants did not receive counseling on nutrition and physical activity during the study period.

Outcomes

The primary outcomes of the study were blood lipids and liver aminotransferase enzymes, which were measured before the intervention, and at 3 and 6 months after the start of the interventions.

Data collection tools & methods

Since lipid, lipoprotein, and liver aminotransferase enzyme tests are conducted annually for employees of Pars Jonoubi Gas Complex in Iran, the medical records of all employees were reviewed, and individuals with abnormalities in these tests were selected. Then, ultrasound imaging was performed by a radiology specialist to diagnose non-alcoholic fatty liver disease (grade 2). Demographic and paraclinical data of the participants were collected in a data collection form.
After a fasting period of 12 to 14 hours, 10 cc of venous blood was drawn, and after serum separation, blood lipid profiles and aminotransferase enzyme levels were measured.
Blood lipids (HDL and LDL) were measured using the Immunoinhibition method, total cholesterol, triglycerides, and fasting glucose were measured using the enzymatic-colorimetric method, and AST and ALT enzymes were measured using the IFCC method enzymatic-colorimetrically using the Pars Azmoon kit (manufactured in Iran) and the Hitachi 902 autoanalyzer (manufactured in Japan) at a wavelength of 340 nanometers and a temperature of 37 degrees Celsius. These measurements were taken 48 hours before the intervention, and then at 3 and 6 months after the intervention. Prior to commencing the experiment, the accuracy of the device was evaluated using the TrueLab N control provided by Pars Azmoon Company. All tests were performed by a skilled technician.

Data analysis

The data were analyzed using SPSS version 21 software, employing descriptive and inferential statistics. Before conducting the main analyses, the distribution of scores for outcome variables was assessed using the Kolmogorov-Smirnov test. Given the normal distribution of the outcome variables, the results of repeated measures ANOVA tests were reported, considering a significance level of less than 0.05. It is worth mentioning that the data analysis was conducted in a blind manner.

Findings

No significant differences were found in these variables between the study groups. In this study, the total population of men with fatty liver was 105 individuals, of which 14 were not willing to participate in the research and 11 did not meet the criteria. Therefore, data related to 80 male employees (Consort diagram) with a mean age of 47.38±7.4 years were analyzed. Among them, 97.5% were married, and 58.8% had educational levels higher than a bachelor's degree. Regarding job type, 58.8% were in administrative positions, with the majority having fixed day shifts.
The results of repeated measures ANOVA showed that although all these lipoproteins improved at 3 and 6 months after the intervention, a significant difference (p=0.005) was only observed in low-density lipoprotein. However, no significant differences were observed in total cholesterol (p=0.4) and high-density lipoprotein (p=0.5) (Table 1). Post hoc test for pairwise comparisons indicates that firstly, these differences were related to the physical activity group coupled with nutritional counseling, and secondly, they were temporally related to 6 months after the intervention.
The results of repeated measures ANOVA indicate that overall, there was no statistically significant difference between groups over time for aspartate aminotransferase (p=0.2). However, a significant difference was observed in alanine aminotransferase (p=0.001) among the study groups (Table 2). Post hoc analysis for pairwise comparisons showed that this difference was attributed to all three intervention groups compared to the control group at both measurement times (three and six months) after the interventions.

Table 1. Comparison of serum levels of total cholesterol and blood lipoproteins among individuals in different groups over measurement times

Group / Subscale/Time	Physical activity group	Nutrition education group	Physical activity group with nutrition education	Control group	Significance level
	(Standard deviation) mean	(Standard deviation) mean	(Standard deviation) mean	(Standard deviation) mean	
Low-density lipoprotein (mg/dL)					

Before intervention	126.7 (27.6)	119.7 (32.2)	127.7 (25.9)	122 (29.8)	0.7
3 months later	104.6 (29.8)	107.5 (30.4)	101.3 (35.5)	117.6 (29.9)	0.4
6 months later	103 (28.3)	104.1 (27.8)	88 (26.7)	113.1 (32.2)	0.005
High-density lipoprotein (mg/dL)					
Before intervention	40 (7.9)	41.3 (9.2)	42.1 (7.8)	41.8 (7.1)	0.8
3 months later	42.1 (8.6)	42.2 (6.8)	43.7 (9.1)	43.6 (7.9)	0.6
6 months later	43.5 (6.8)	48.2 (38.9)	45.3 (8.2)	41.4 (6.9)	0.8
Total cholesterol (mg/dL)					
Before intervention	203.5 (33.8)	194.5 (36.6)	193.8 (38.3)	191.1 (52.3)	0.7
3 months later	183.4 (31.9)	186.7 (31.8)	185.5 (37)	196.3 (30.4)	0.6
6 months later	183.6 (29.1)	180 (30.7)	177.1 (31.7)	187 (26.3)	0.7

Table 2. Comparison of serum levels of liver aminotransferase enzymes among different groups at measurement times

Liver enzyme / Measurement time	Physical activity group	Nutrition counseling group	Physical activity group combined with nutrition counseling	Control group	Significance level
Alanine Aminotransferase (IU/L)					
Before intervention	39.6 (19.4)	44.1 (18.5)	48.1 (30.7)	52.3 (30.7)	0.3
Three months later	40.1 (18.1)	37.5 (14.6)	33.7 (14.5)	57.2 (21.4)	0.001
Six months later	36.1 (19.6)	32.9 (15.4)	29.5 (19.8)	57.9 (17.3)	0.001
Aspartate Aminotransferase (IU/L)					
Before intervention	24.1 (8.9)	27.9 (9.2)	33.7 (14.7)	30.4 (10.6)	0.06
Three months later	24.7 (8.1)	26.4 (7.9)	24.1 (7.9)	30 (9.1)	0.1
Six months later	28.6 (12.2)	27.5 (9.6)	23.3 (8.8)	31.7 (8.5)	0.09

Discussion

There was no significant improvement in the liver enzyme AST, but serum ALT levels in all three interventions groups-physical activity, nutrition education, and combined physical activity with nutrition education showed significant improvement compared to the control group at both 3 and 6 months after intervention.

Regarding significant reduction in AST and the lack of significant difference in ALT, the findings of this study is contrast with the studies by Behzadi Moghadam (2018) [24] and Hallsworth [25] where only AST showed a significant reduction after 8 weeks of exercise, while ALT remained unchanged. In the study by Hassani *et al.* (2016), serum levels of AST and ALT significantly decreased after 8 weeks of exercise in patients with fatty liver disease [26]. In the study by Gelli *et al.* (2017), after 8 weeks of aerobic exercise and the use of milk thistle extract supplement, all three liver enzymes significantly decreased during treatment in women with fatty liver, and significant improvements were observed in AST, ALT, GGT, HDL, serum glucose, LDL/HDL, TG/HDL, and NAFLD liver fat score between the start and end of treatment [1]. The difference in the results of the current study and the aforementioned study could be due to the addition of milk thistle intervention. Additionally, Shamseddini *et al.* (2015), contrary to the current study, concluded that aerobic and resistance exercises can reduce liver enzyme levels in patients with non-alcoholic fatty liver disease [12]. However, Skrypnik *et al.* (2016) reported that combined strength and endurance training had a greater positive effect on improving liver fat and reducing ALT and AST enzymes compared to endurance training alone [27]. In the current study, only ALT in the physical activity group showed a significant improvement compared to the control group, while AST did not show a significant improvement. Considering the results of the Skrypnik study and since the exercise in this study was aerobic, it may be inferred that endurance exercise alone is not effective for improving liver enzymes, and both combined strength and endurance exercises should be used. Centis *et al.* reported that patients with non-alcoholic fatty liver disease have little readiness for physical activity change, with 50% categorized as pre-contemplative or contemplative, meaning resistant to increasing exercise [28]. One of the possible reasons for the lack of improvement in AST in patients under each intervention in this study was that although ultrasound confirmed grade 2 fatty liver in intervention groups, the patients' liver enzymes were within normal range, and we should not expect further

reduction. Furthermore, the researcher did not have complete control over the participants' nutrition. However, the reduction in AST in the physical activity combined with nutrition education group is evident, which, although not statistically significant, is clinically valuable.
The findings of this study indicate that HDL and total cholesterol did not show significant improvement after the interventions. However, LDL showed significant improvement after 6 months of intervention, with this improvement being significant in the physical activity combined with nutritional education group. Consistent with the present study, Hosseini *et al*. (2014) found that the combination of nutrition and physical exercise has a significant effect on lipids. In Hosseini's study, a significant reduction in total cholesterol, triglycerides, and LDL was observed in the nutrition and exercise group [20]. However, Monserrat-Mesquida *et al*. (2022) also demonstrated that the Mediterranean diet group combined with exercise had a greater weight loss and reduction in triglycerides compared to the control group [29]. In the present study, after the other interventions of physical activity and nutritional education, improvements in LDL, HDL, and total cholesterol were observed after each of three interventions, but these differences were not statistically significant, which can still be clinically relevant. Ghorbanian *et al*. (2015) found that fasting blood sugar, HDL, and LDL levels did not show significant differences between the two groups after 8 weeks of training, but total cholesterol and triglycerides were significantly lower in the exercise training group compared to the control group [30]. Although some results of this study were similar to the present study, there are differences regarding total cholesterol, triglycerides, and LDL. Since the intensity and volume of exercises have a significant impact on ApoA-1, HDL, and LDL, this difference can be justified, as the intensity and volume of exercises in the present study were higher and supervised by the researcher, resulting in a significant decrease in LDL. This is supported by the study conducted by Shearman *et al*., where they demonstrated that using a low-intensity endurance exercise protocol (50 to 60 percent of maximum heart rate) on adult men showed negligible changes in ApoA-1, HDL, and LDL after six weeks, but significant changes in both factors were observed after fourteen weeks [31]. Furthermore, in this study, LDL did not show improvement after 3 months, but it showed significant improvement after 6 months, indicating that the longer the interventions, the greater the possibility of improvement in lipoproteins. According to the results of the present study, no significant difference was observed in other blood lipids after the intervention. Lack of complete control over adherence to the diet and even the intensity of exercise may be among the possible reasons for the lack of effect of exercise and nutritional education and their combination on these variables.
In the examination of the timing, in the group receiving physical activity combined with nutritional counseling, there was a significant reduction in low-density lipoprotein (LDL) in the sixth month after the start of the interventions, while the changes in the third month were not significant. However, ALT showed a significant reduction at both 3 and 6 months after the intervention, although this reduction was greater after 6 months. It seems that the longer the duration of exercise and nutritional interventions, the greater the improvement in LDL, AST. Therefore, maintaining a healthy lifestyle throughout life may contribute to the prevention and treatment of fatty liver.
One strength point of this study was the researcher's control over participants' physical activity due to their collaboration with them. However, the present study also had some limitations. Due to the inability to directly control participants' nutrition by the researcher, especially the use of self-service and workplace cafeteria, participants did not have the full opportunity to adhere to the nutritional interventions. Another limitation was the lack of initial alignment between ultrasound findings and liver enzymes, and since ultrasound is the gold standard for diagnosing fatty liver, patients were enrolled in the study based on confirmed fatty liver in their ultrasound. It seems that the number of patients studied for this research was low, and there would have been more significant changes in the study's parameters with a larger sample size.

Conclusion
The study demonstrated that lifestyle improvements, including physical activity and adherence to a balanced diet, can lead to a reduction in liver enzyme ALT and LDL in patients with non-alcoholic fatty liver disease. When used in combination, especially for a duration of 6 months or more, the interventions will have a more effective efficacy.
Due to the limitations of the aforementioned study, it is recommended that further research be conducted with a larger sample size in a diverse population. This population should include

individuals diagnosed not only with fatty liver on ultrasound but also with liver enzyme abnormalities.

Therefore, based on the results of the current study, it is suggested that healthcare professionals and health team members implement this protocol, which includes a healthy diet pattern along with regular brisk walking, in educational and preventive programs for individuals predisposed to obesity and fatty liver, as well as patients diagnosed with fatty liver.

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Authors' contributions

Hooman Jamshidi: First Author/Main Researcher/Study Design/Introduction Writer/Discussion Writer (30%); **Janmohammad Malekzadeh**: First Author/Assistant Researcher/Methodologist/Statistical Analyst/ (10%); **Ardeshir Afrasiabifar**: First Author/Assistant Researcher/Methodologist/Statistical Analyst/Discussion Writer (10%); **Ali Karam Alamdari**: First Author/ Main Researcher/Study Design/Introduction Writer/Discussion Writer (30%); **Hajar Zamani Habibabadi**: First Author/Assistant Researcher/Introduction Writer/ Discussion Writer (10%); **Nazafarin Hosseini**: First Author/Assistant Researcher/Methodologist/Introduction Writer/Discussion Writer (10%).

All authors reviewed and approved the final version.

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Data Availability

The dataset generated and analyzed during the current study is available from the corresponding author upon reasonable request.

Ethical observations

Research on human subjects was conducted according to the Helsinki Declaration. The study was approved by the ethics committee of Yasuj University of Medical Sciences with the ID IR.YUMS.REC.1396.189. Participants were informed about the research objectives, and written informed consent was obtained from them. Additionally, they were assured that their personal information would remain confidential and would not be disclosed. At the end of the study, educational materials were provided to the participants in the control group. No expenses were imposed on the participants.

Conflict of Interest

The authors declare that this research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

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Figure 1: Consort Table