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Original Article

Effect of aerobic and resistance exercise on liver enzyme and blood lipids in Chinese patients with nonalcoholic fatty liver disease: a randomized controlled trial

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Abstract: Aim: The study aimed to evaluate the effect of aerobic and resistance exercise on ALT and blood lipids in Chinese patients with Nonalcoholic Fatty Liver Disease. Methods: In this randomized controlled trial, 103 patients with clinically defined NAFLD were randomly assigned to aerobic exercise (n=34), resistance exercise (n=34) or non-exercising control (n=35) for 22 weeks interventions. All patients were received diet education. An aerobic group program consisted of 60 minutes aerobic exercise at 60%-70% maximum heart rate intensity, a resistance group performed 3 series of 10 repetitions at intensity of 60%-70% of 1 repetition maximum (1RM) for 60 min/d and the control had no training program during the study. Results: Ninety-one of the 103 participants (29, 31 and 31 in the aerobic, resistance and the control groups, respectively) were eventually included in data analysis. There were no adverse events. At baseline, the clinical characteristics were matched among the three groups. After 22 weeks, compared with the control group, a significant improvement in HDL was observed in both the aerobic and resistance exercise groups (P=0.005; P=0.009). In the aerobic group, the levels of alanine aminotransferase (ALT) and Triglycerides (TG) were decreased significantly (P=0.007; P=0.046), and the level of HDL was improved significantly (P=0.049) compared to the baseline. In the resistance group, HDL was increased significantly (P=0.027). Conclusions: This study demonstrated that both aerobic and resistance exercise alone are effective in improving HDL among Chinese patients with NAFLD. Aerobic exercise but not resistance training can reduce the levels of ALT and TG.

Keywords: Aerobic exercise, resistance exercise, liver enzyme, blood lipids, nonalcoholic fatty liver disease

Introduction

Non-alcoholic fatty liver disease (NAFLD) involves a spectrum of conditions ranging from benign hepatic steatosis to non-alcoholic steatohepatitis (NASH). Those with steatohepatitis can progress to cirrhosis and even liver failure [1-4]. NAFLD is the most widespread form of chronic liver disease in developed countries [5-7], with an overall prevalence of NAFLD in western countries of 20-30% [8]. In China, approximately 20% of adults in the general population have NAFLD [9]. NAFLD is typically accompanied by elevated liver enzymes including alanine amino transferase (ALT) and aspartate amino transferase (AST) [10], and dyslipidemia with elevated levels of Triglycerides (TG), total cholesterol (TC) and low-density lipoprotein (LDL), whereas decreased high density lipoprotein (HDL) cholesterol [11-15]. Nonalcoholic fatty liver disease is closely associated with metabolic risk factors (hypertension, dyslipidemia, hyperglycemia) [16], and it is also related to an increased risk of cardiovascular disease independent of metabolic risk factors [17]. Sedentary lifestyle is a well-established risk factor for NAFLD [18].

Exercise plays a pivotal role in the management of NAFLD and is being increasingly studied regarding the effects on liver fat even without significant of weight loss [19], which is a primary part of treatment for NAFLD as recommended by the American Gastroenterological Association [20] as well as the American Association for the Study of Liver Diseases [18]. It has been reported that aerobic exercise improves serum liver enzymes and modulates hepatic lipid metabolism, reducing aminotransferase levels and hepatic fat accumulation, affecting very low-density lipoproteins (VLDL) secretion [21-24]. Moreover, resisitance training can decrease cardiovascular risk factors, improving cardiorespiratory fitness [25] and reducing Hepatic Fat Content [26] as well. However, few studies have focused on the effect of resistance exercise on the liver enzyme and blood lipid in Chinese patients with NAFLD. Therefore, we conducted a randomized controlled clinical trial study to evaluate the effectiveness of aerobic exercise and resistance training on liver enzyme (ALT) and blood lipids among the Chinese patients with NAFLD.

Methods

Participants

In the study, subjects were enrolled from Jiangsu Province Hospital of Integration of Chinese and Western Medicine and Danyang central hospital, China. Inclusion criteria were consistent with the 2010 edition of guidelines for the diagnosis and treatment of NAFLD; with grade five muscle strength; without regular exercise; aged between 18 and 75 years; patients were conscious and with the ability of communication. The exclusion criteria were identified as a variety of acute and chronic infections, cancer, and other immune diseases; serious acute and chronic diseases, such as acute cerebral infarction, lumbar disc herniation; proliferative retinopathy; pregnant or lactating women; long term drinking history defined as a long history of alcohol consumption for more than 5 years, which was equivalent to the amount of male alcohol more than 140 g/weeks and the amount of female ethanol greater than 70 g/weeks; had no history of viral and autoimmune hepatitis, and drug-induced liver diseases. Participants who did not take part in training more than two times a week and for whom telephone notification was not effective in convincing subjects to participate were dropped from the study. Patients were randomly divided into three groups including aerobic, resistance and control group by sealed envelopes. The intervention lasted for five months.

Eligible patients signed a written informed consent before participating in the study. All methods were carried out in accordance with the approved guidelines and regulations.

Study measurements

Anthropometric and blood pressure: The height (centimeters) and weight (kilograms) of patients were measured using the body composition analyzer (Brand: yuyue; model: SK-X80/TCS-160D-W/H) and non-elastic tape. Body mass index (BMI) was calculated by the Quetelet index using formula: weight (kg)/height (m)^2. Patients wearing light clothes, in bare feet and standing on the body composition analyzer were measured, each time using the same instrument. Waist circumference and hip circumference were measured using a non-elastic tape measure. Blood pressure was measured using Mercury electronic sphygmomanometer (Brand: yuyue; model: YE660C). In addition, patients avoided strenuous exercise and hot drinks in half an hour before the measurement of blood pressure. When measuring the arterial blood pressure patients were seated and blood pressure was measured in the right upper arm to ensure the right brachial artery and heart at the same level.

Biochemical index: Biochemical index (fasting plasma glucose and fasting insulin, blood lipid and liver enzyme) were measured using Roche automatic asnalyzer. After an overnight fast of (>10 h) venous blood was collected from the antecubital vein. Blood analysis was performed on the same day as collection for fasting plasma glucose, fasting insulin and blood lipids (including total cholesterol (TC), Triglycerides (TG), high density lipoprotein cholesterol (HDL-C), and low density lipoprotein cholesterol (LDL-C)) and liver enzymes were determined using alanine aminotransferase (ALT).

Diet

All participants received diet education by a dietician. Participants were encouraged to follow a healthy diet, according to the 2010 edition guidelines for the diagnosis and treatment of NAFLD.

Aerobic exercise

During the 22-week intervention period, aerobic exercise consisted of three phases: warming-up (5 min), training (50 min) and relaxing (5 min). Aerobic exercise progressed from 40 min per day at 45%-55% maximum heart rate intensity in the initial stage of training (within 2 weeks) gradually increase to 60 min per day at 60%-70% maximum heart rate intensity. Exercise was performed three times per week on non-consecutive days for 22-week. Patients who attended 66 times or more in 22-week were considered to have finished the study. An Accredited Exercise Specialist supervised the training. Heart rate and blood pressure were continuously monitored to ensure the subject's exercise intensity achieved the appropriate intensity. All the participants came to centers carried out the exercise under the guidance of professional personnel.

Resistance exercise

Elastic band was used as the load instrument during the 22 weeks resistance intervention period. Resistance training consists of three phases: warm up (5 min joint movement), training (50 min), and relaxing (5 min). Participants performed the training from 3 series of 8 repetitions at intensity of 30%-40% of 1 repetition maximum (1RM) for 40 min per day in the early stage of the exercise (within 2 weeks) gradually move to 3 series of 10 repetitions at intensity of 60%-70% 1RM for 60 min per day, with one minute of recovery between series. The exercise was performed three times per week on non-consecutive days for 22 weeks. The load gradually increased depending on the individual ability of the subject and with consultation of professional personnel. Participants were considered to have finished the study if they attended 66 times or more in 22 weeks. All participants came to centers carried out the exercise under the guidance of professional personnel as well.

Control

Control subjects were asked to maintain their daily physical activity (no participation in structured physical activities) during the 22-week period of the study. Participates were taught about the pathogenesis of NAFLD and the current treatment of the disease. Simultaneously, they were asked diet and exercise habits, and instructed the importance of lifestyle intervention. According to the standards of Chinese dietary guidelines, participants were conducted a unified diet education by dietician in the form of Seminar once a month. Telephone follow-up once a month included assessment of participant specific diet and physical activity, for 22 consecutive weeks.

Safety assessment

Participants were given a load test at baseline, testing the maximum strength and the process was carried out under the guidance of professionals. Together they performed the training of 3 times per week under the supervision of the medical staff during the entire study. At the end of each exercise, we measured the pulse for each patient in 30 seconds; the heart rate and exercise intensity were monitored in time and adjusted according to the results.

If the participant had an adverse event such as low back pain and shoulder pain occurred, we contacted the doctors in the research group. In addition, participants were considered to drop out if they could not continue to participate in exercise because of the pain.

Statistical analysis

Mean ± SD was used to describe continuous variables, and categorical variables were presented as number (percentage). Descriptive statistics were used to analyze demographic and clinical variables. Paired t-tests were used to assess within group changes from baseline to end of intervention. Continuous variables with normal distribution and homogeneity of variance were evaluated using an unpaired t-test, otherwise the Wilcoxon rank non-parametric test was performed. Comparison of measurement data with normality between groups were tested by One-Way ANOVA analysis, the homogeneity of variance was compared by LSD or SNK method, or Welch approximate variance analysis was used. *P* values of less than 0.05 were accepted to indicate statistical significance. All data were analyzed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA).

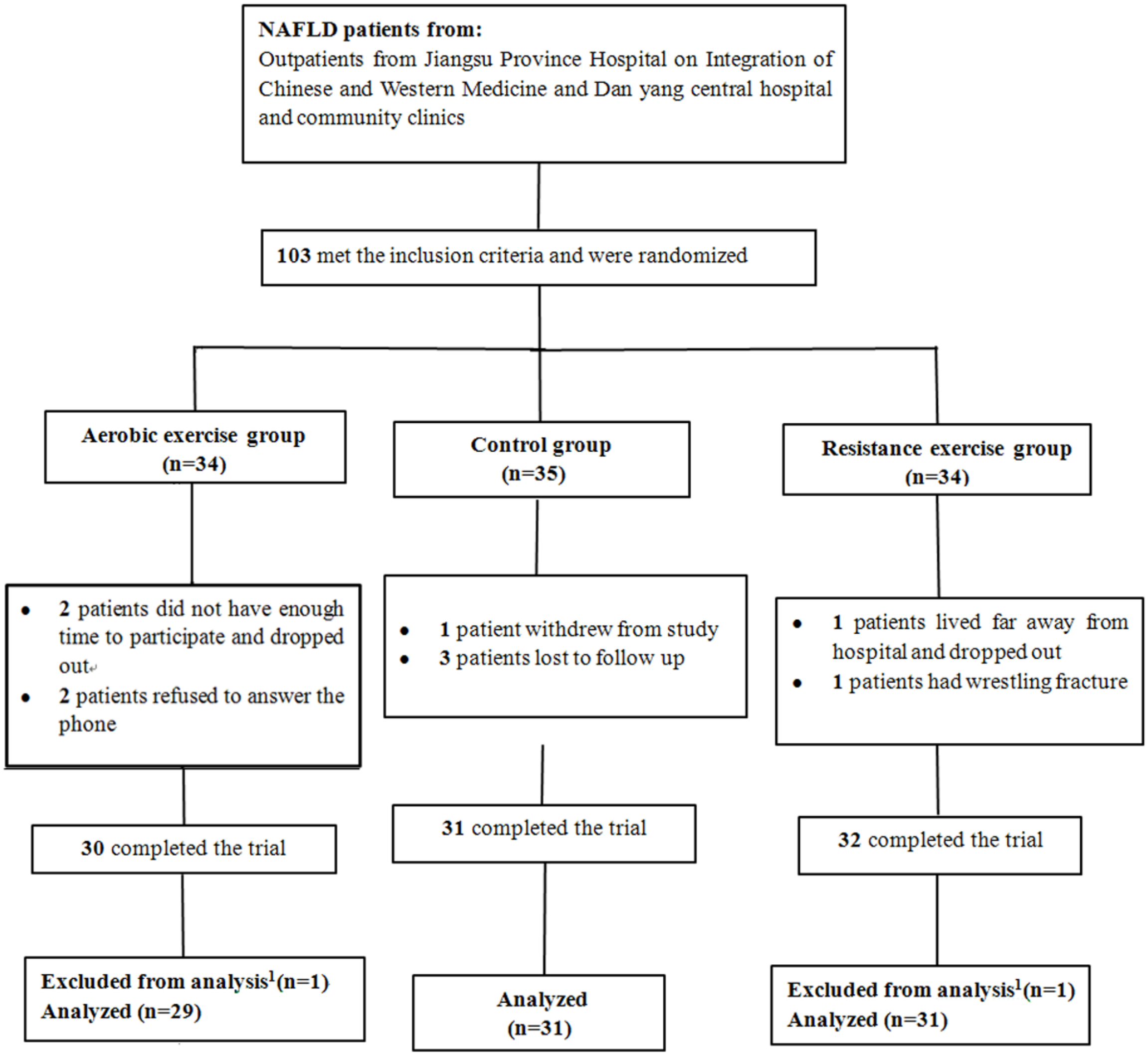

Figure 1. Excluded from analysis because the exercise sessions they participated were less than 46 times. NAFLD: Non-alcoholic fatty liver disease.

Results

As presented in **Figure 1**, 103 NAFLD patients were initially recruited to the study. Thirty-four were randomly allocated to the aerobic exercise group. Thirty (88%) patients completed the 22-week exercise program. Thirty-four participants were randomized to the resistance exercise group and in this group 32 (94%) patients completed the study. Thirty-five subjects were assigned to the control group of which 31 (89%) finished the study. Two subjects (one each in aerobic and resistance groups) were excluded from statistical analysis because the exercise sessions they participated were less than 46 times (the total training sessions was 66 times). Therefore, 91 subjects, 36 (39.56%) males and 55 (60.43%) females, were included in the final data analysis. There were 29 patients in aerobic group, 31 patients in resistance group, and 31 patients in control group.

No statistical difference was found among the three groups in baseline characteristics (**Table 1**).

As shown in **Table 2**, the levels of TG and ALT were significantly decreased (P=0.046, P=0.007), whereas the HDL level was significantly increased (P=0.049) in aerobic group after training. In resistance group, HDL was significantly improved (P=0.027), but other metrics did not change significantly. However, in the control group no statistical difference was found in TG, ALT, HDL, TC, LDL, blood glucose and FI after training.

Table 1. Main baseline characteristics of the subjects enrolled in the study (Mean ± SD)

Variables	Aerobic (n=29)	Resistance (n=31)	Control (n=31)	F/chi-square	P
Age y	61.28±7.52	55.80±12.29	58.06±9.79	2.165	0.121
Gender (Male/female)	7/22	16/15	13/18	5.246	0.073
Anthropometry					
BMI (kg/m2)	25.46±2.51	26.86±3.62	26.46±3.88	1.134	0.320
Waistline (cm)	92.48±8.93	92.12±8.59	92.07±10.69	0.014	0.987
Waist Hip Rate	0.95±0.08	0.92±0.05	0.93±0.06	1.072	0.351
Blood pressure					
Systolic BP (mmHg)	135.04±13.60	131.23±18.29	134.59±14.07	0.484	0.618
DiastolicBP (mmHg)	80.22±9.48	80.73±12.79	83.00±9.20	0.553	0.577
Blood glucose and insulin function					
FBG (mmol/l)	6.57±1.43	6.52±1.24	6.21±1.45	0.579	0.562
FI (mU/l)	12.86±3.74	14.67±7.52	11.41±3.84	2.630	0.079
Blood lipid					
TC (mmol/l)	5.23±1.48	4.86±1.05	4.64±0.87	1.899	0.156
TG (mmol/l)	3.06±2.86	2.49±2.12	2.96±1.35	0.540	0.585
HDL-C(mmol/l)	1.21±0.31	1.17±0.30	1.08±0.24	1.493	0.231
LDL-C (mmol/l)	3.01±1.05	3.06±1.06	2.90±0.86	0.193	0.825
Liver function					
ALT(U/L)	26.89±12.68	29.60±14.89	24.31±13.87	1.020	0.365

BMI: body mass index; FBG: Fasting Blood Glucose; FI: Fasting Insulin; TC: Total Cholesterol; TG: Triglyceride; HDL-C: High Density lipoprotein cholesterol; LDL-C: Low Density Lipoprotein cholesterol; ALT: Alanine Aminotransferase.

Table 2. Blood Lipids and Liver Enzyme and blood glucose and Fasting insulin changes Observed After 22 weeks Training Intervention in Three Groups[a,b]

Variables	Aerobic (n=29)			Resistance (n=31)			Control (n=31)			F	P
	Baseline	Posttest	P	Baseline	Posttest	P	Baseline	Posttest	P		
BMI	25.51±2.30	25.31±2.08	0.237	26.82±3.72	26.73±3.61	0.713	26.66±4.13	26.73±4.11	0.585	1.989	0.144
WHR	0.95±0.08	0.91±0.08	0.048	0.92±0.05	0.91±0.05	0.309	0.93±0.06	0.92±0.06	0.169	0.144	0.866
TC	5.23±1.48	5.13±0.92	0.714	4.86±1.05	4.87±0.83	0.946	4.68±0.86	4.73±0.88	0.700	1.676	0.193
TG	3.06±2.86	2.10±1.07	0.046	2.49±2.12	2.20±1.14	0.411	3.00±1.36	2.62±1.35	0.146	1.357	0.263
HDL	1.21±0.31	1.29±0.33	0.049	1.17±0.30	1.24±0.29	0.027	1.09±0.24	1.03±0.25	0.096	5.197	0.007
LDL	3.01±1.05	3.24±0.98	0.093	3.06±1.06	3.19±0.65	0.420	2.92±0.87	3.07±0.79	0.237	0.532	0.590
ALT	26.89±12.68	18.79±9.62	0.007	30.38±14.60	24.23±14.31	0.054	24.31±13.87	20.03±9.29	0.134	0.895	0.412
FBG	6.57±1.43	6.40±1.49	0.392	6.52±1.24	6.31±1.36	0.285	6.21±1.45	6.39±1.85	0.448	0.026	0.974
FI	12.86±3.74	12.75±3.46	0.876	14.67±7.52	12.86±4.46	0.095	11.41±3.84	11.25±3.53	0.641	1.420	0.247

[a]Abbreviation: TC: Total Cholesterol; TG: Triglyceride; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein; ALT: Alanine Aminotransferase, FBG: Fasting Blood Glucose. FI: Fasting Insulin [b]Values are presented as Mean ± SD.

After 22-week, difference value of HDL among three groups reached statistical difference (P=0.008) (**Table 3**). Compared with the control group, a significant improvement in HDL was observed in both aerobic exercise group and resistance exercise group after 22-week (P=0.005, P=0.009) (**Figure 2**).

Adverse events

No adverse events were reported throughout the study, one participant in the resistance exercise group had bone fractures caused by falling down but it did not occur during exercise sessions.

Discussion

Researchers have not found the best type of exercise nor the most appropriate amount of exercise for NAFLD [27]. In this study, we compared the effects of aerobic and resistance exercise on liver enzymes and blood lipids among Chinese patients with NAFLD. The pri-

Table 3. Blood Lipids and Liver Enzyme changes observed after 22 weeks Training interventions between groups[a,b]

Variables	Aerobic (n=29)	Resistance (n=31)	Control (n=31)	F	P
	d	d	d		
TC	-0.10±1.39	0.01±0.73	0.06±0.77	0.171	0.844
TG	-0.96±2.43	-0.29±1.81	-0.38±1.37	1.001	0.372
HDL	0.08±0.21	0.07±0.16	-0.06±0.19	5.146	0.008
LDL	0.23±0.71	0.13 ±0.84	0.15±0.68	0.139	0.870
ALT	-8.11±14.81	-6.15±15.49	-4.28±14.90	0.461	0.632

[a]Abbreviation: d, d is differences between post and baseline; TC: Total Cholesterol; TG: Triglycerides; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein; ALT: Alanine Aminotransferase. [b]Values are presented as Mean ± SD.

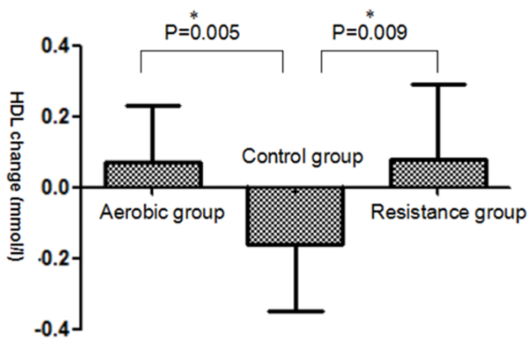

Figure 2. Effect of aerobic or resistance exercise on the level of HDL. The difference value of HDL Changes observed after exercise among three groups. Data are presented as Mean ± SD. *significantly different from control group (P<0.05).

mary finding of this study is that both aerobic exercise and resistance exercise, which performed for 180 min per week, resulted in an improvement in HDL level among the patients with NAFLD. This result was partially consistent with previous studies. A meta-analysis of 52 aerobic exercise trials of >12 weeks'duration including 4700 participants demonstrated an average increase in HDL level of 4.6% [28]. Couillard et al. [29] also reported that five months regular aerobic exercise improves HDL that is followed by reduce in the level of triglyceride. However, we did not find a resistance exercise trial that lasted for 22-week. A meta-analysis of twenty-nine resistance exercise randomized controlled trials of ≥4 weeks' duration including 1329 patients revealed a significant improvement in HDL levels, in which the maximum duration of resistance exercise was 4 months [30]. Comparisons between aerobic and resistance exercise groups in the current study suggested that aerobic exercise, as well as resistance exercise, markedly increase HDL in Chinese patients with NAFLD. The result provides a helpful alternative in patients whom aerobic exercise may not be approachable, as the high cardiorespiratory demand characteristic of this type of exercise is closely related to fatigue and discomfort [26].

In this study, we also found that aerobic exercise significantly reduced ALT and TG. Similar findings have been reported in previous studies regarding relationship between aerobic training and ALT [31] and the relation between physical activity and ALT in patients with NAFLD [32]. Davoodi et al. [33] revealed that ALT levels were reduced after 8 weeks of aerobic exercise. Chalamalasetty et al. [4] also reported that moderate intensity aerobic exercise helps in normalizing ALT levels in patients with nonalcoholic steatohepatitis. Couillard et al. [29] have already shown that regular aerobic exercise training may be particularly helpful in men with elevated TG, aerobic exercise has been shown to reduce intrahepatic TG and visceral fat even in the absence of significant weight changes [34], the results of these studies are in accordance with our findings. Our study demonstrated that aerobic exercise induces decreases in ALT and TG that were more apparent than resistance exercise.

The current study has major strengths that the duration of resistance exercise for 22-week, which was relatively longer, and the direct supervision of physical exercise sessions by researchers. Notwithstanding these strengths, one limitation of this study should be noted. The sample size was relatively small. And larger sample size studies should be carried out in the future.

The results of this study indicated that 22-week of aerobic exercise and resistance training were effective in improving HDL levels, whereas aerobic exercise might have additional benefits in reducing the level of liver enzyme (ALT) and TG in Chinese patients with NAFLD. However, the longer time effect of training in the clinical management of such patients will depend upon long-term maintenance and sustainability of exercise, which warrants further studies.

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Disclosure of conflict of interest

None.

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