

Effect of resistance training on non-alcoholic fatty-liver disease a randomized-clinical trial

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Abstract

AIM: To evaluate the effect of resistance training (RT) on non alcoholic liver disease (NAFLD) patients.

METHODS: A randomized clinical trial enrolling NAFLD patients without secondary liver disease (*e.g.*, without hepatitis B virus, hepatitis C virus or excessive alcohol consumption). Patients were randomly allocated either to RT, three times weekly, for 3 mo or a control arm consisting of home stretching. The RT included leg press, chest press, seated rowing, latissimus pull down

etc. with 8-12 repetitions, 3 sets for each exercise, for a total duration of 40 min. Hepatic ultrasound, fasting blood tests, anthropometrics and body composition by dual energy X-ray absorptiometry were assessed. At baseline and follow-up, patients filled out a detailed semi-quantitative food frequency questionnaire reporting their habitual nutritional intake. Steatosis was quantified by the hepatorenal-ultrasound index (HRI) representing the ratio between the brightness level of the liver and the right kidney. The HRI has been previously demonstrated to be highly reproducible and was validated against liver biopsy and proton magnetic resonance spectroscopy.

RESULTS: Eighty two patients with primary NAFLD were randomized to receive 3 mo of either RT or stretching. After dropout or exclusion from analysis because of protocol violation (weight change > 3 kg), thirty three patients in the RT arm and 31 in the stretching arm completed the study per protocol. All baseline characteristics were similar for the two treatment groups with respect to demographics, anthropometrics and body composition, blood tests and liver steatosis on imaging. HRI score was reduced significantly in the RT arm as compared to the stretching arm (-0.25 ± 0.37 vs -0.05 ± 0.28 , $P = 0.017$). The RT arm had a significantly higher reduction in total, trunk and android fat with increase in lean body mass. There was no correlation between the reduction in HRI in the RT arm and weight change during the study, but it was positively correlated with the change in trunk fat ($r = 0.37$, $P = 0.048$). The RT arm had a significant reduction in serum ferritin and total cholesterol. There was no significant difference between arms in dietary changes and these did not correlate with HRI change.

CONCLUSION: Three months RT improves hepatic fat content accompanied by favorable changes in body composition and ferritin. RT may serve as a complement to treatment of NAFLD.

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Key words: Resistance exercise; Obesity; Nutrition; Physical activity; Abdominal fat

Core tip: Resistance training is viewed as a complement to aerobic training. However, data on the effect of resistance training on non alcoholic liver disease (NAFLD) is scant. A three month resistance training in NAFLD patients exerted a significant reduction in liver fat as well as reduction in total body and trunk fat with increase in lean body mass. Furthermore, resistance training led to reduction in serum ferritin and cholesterol. In NAFLD patients, compliance to aerobic training may be low due to fatigue. Therefore, resistance training can serve as an easier alternative or a complement form of exercise in these patients.

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INTRODUCTION

Lifestyle modifications, including weight reduction and physical activity, improve many of the risk factors for non alcoholic liver disease (NAFLD)^[1] and have become the primary treatment modalities for the disease^[2]. The role of physical activity (PA) as a potential treatment for NAFLD has been tested in several observational studies and a few clinical trials, mostly testing the effect of aerobic training. Resistance training (strength training) is a means for developing and maintaining muscular strength, endurance, power, and muscle mass that has grown in popularity over the past two decades^[3,4]. In a study of the general population, resistance training (RT) was inversely associated with NAFLD. This association remained significant after adjusting to multiple confounders including body mass index (BMI), homeostasis model assessment (HOMA), nutritional factors, adiponectin, and resistin^[5]. Two small trials found beneficial effects for RT as a single treatment in NAFLD patients, but results regarding reduction in steatosis were conflicting^[6,7]. In a randomized clinical trial (RCT) in 19 sedentary adult NAFLD patients, 8 wk of RT, consisting of 45 min sessions three times weekly, led to a reduction in liver fat without weight loss^[7]. In an uncontrolled clinical trial in 12 obese adolescents, a three-month RT program consisting of 1 h sessions twice weekly did not change hepatic fat content but improved hepatic insulin sensitivity^[6]. In a recent RCT among type-2 diabetic patients, it was demonstrated that resistance training and aerobic training are equally ef-

fective in reducing hepatic fat content^[8].

NAFLD patients report a poorer health-related quality of life compared with healthy United States population both on physical and mental health scores^[9]. Furthermore, fatigue is a common symptom in NAFLD patients^[10], and they report low scores for vitality^[9]. Although NAFLD patients understand the benefits of exercise, they lack the confidence to perform it and express a fear of falling^[11]. The potential benefits of RT are not only to cardiovascular health and to weight management but it also improves balance and reduces the risk of falls^[12-14]. RT improves several components of physical function, contributes to health-related quality of life^[15,16], and is well tolerated even among patients with coronary heart disease or the elderly^[15,17]. In recent years, increasing attention has been paid to RT as a useful adjunctive tool of exercise in various metabolic diseases including diabetes and heart disease^[4,18,19]. Indeed, the American Heart association and American College of Sport Medicine (ACSM) recommend RT at least twice a week in addition to aerobic training^[4]. For those patients who may have physical limitation or low motivation that prevents them from performing aerobic PA, RT can serve as an alternative option.

Therefore we conducted a randomized controlled trial of RT *vs* stretching. Our main aim was to evaluate the effect of 3 mo RT on the presence of fatty liver measured by abdominal ultrasound and on the hepatorenal index (HRI) as a quantitative objective measurement of steatosis. We also evaluated the effect of the RT program on liver enzymes, metabolic parameters and body composition.

MATERIALS AND METHODS

We conducted a RCT (sealed envelopes randomization stratified by gender) in consecutive patients with ultrasound diagnosed fatty liver attending the liver clinic at the Tel-Aviv Medical center during 2010-2012 and community regional HMO's clinics. Inclusion criteria were age between 20-65 years and a diagnosis of fatty liver by ultrasound in the past 6 mo and on the baseline US examination. Exclusion criteria were any known secondary liver disease including the presence of hepatitis B surface antigen or anti-hepatitis C virus antibodies, excessive alcohol consumption defined as ≥ 30 g/d in men or 20 g/d in women, administration of medical treatment that may elevate alanine aminotransferase (ALT) or lead to hepatic steatosis, known diabetes, major chronic diseases including: renal, cardiovascular, lung, uncontrolled hypertension, inflammatory bowel disease, active cancer, autoimmune disorders and orthopedic contraindications for RT. Adults with diabetes were excluded to avoid a confounding effect, since it is unclear whether they would have the same response to physical training and since changes in antidiabetic medications during the trial might occur. We also excluded patients regularly performing RT in the 3 mo or 6 mo prior to

study enrolment for novice and progressive trainee respectively (novice-trained continuously less than 2 mo, progressive-trained continuously more than 2 mo). Patients performing vigorous aerobic PA in the 3 mo prior to the study, defined as aerobic exercise ≥ 5 d a week 30 min at moderate pace or 3 d a week 20 min at vigorous pace or 4 times a week with combination of both and patients with recent weight reduction (more than 3 kg in the last 3 mo) were also excluded.

A sample size of 32 patients in each group was calculated to be needed for a 90% power to detect a difference of 0.25 with a standard deviation of 0.30, based on previously published data on HRI change following weight change^[20], with a 0.050 two-sided significance level. Additional 20% patients were recruited taking into consideration attrition or protocol violation.

The study was approved by the Tel-Aviv Medical center ethics committee and all patients signed an informed consent. The study was pre-registered in the NIH registration website (TRIAL no. NCT01264198).

Lifestyle and medical evaluation

Each patient underwent at baseline a face-to-face interview by the same trained interviewer. The questionnaire was assembled by the Israeli center for disease control and was used in the first Israeli National Health Survey. It consists of structured questions about alcohol consumption, medications and medical history. PA evaluation was performed by a questionnaire that was tailored and validated for the Israeli population^[21], according to which a summarized index of all questions was calculated and used as an indicator of PA levels.

At baseline, patients filled out a detailed semi-quantitative food frequency questionnaire (FFQ) reporting their habitual nutritional intake in the past year. The FFQ was assembled by the Food and Nutrition Administration, Ministry of Health and was previously described in detail^[5,22,23]. The FFQ is composed of 120 food items with specified serving sizes or standard weight and volume measures of the servings commonly consumed in this study population. The nutrient components of each food item were taken from the Israeli National Nutrient Database. At the end of the trial patients filled out the same FFQ but reported their nutritional intake in the past 3 mo in order to evaluate changes in nutritional habits during the trial.

Blood pressure was measured by an experienced nurse following a uniform protocol. Each participant underwent biochemical testing, following a 12 h fast, for liver enzymes, serum lipid profile, and fasting serum glucose and insulin levels. The HOMA was calculated as fasting [serum insulin ($\mu\text{U/mL}$) \times fasting plasma glucose (mmol/L)]/22.5.

Ultrasonographic examination for determination of NAFLD and quantification of steatosis

Fatty liver was assessed by abdominal ultrasonography using standardized criteria^[24]. Ultrasonography was per-

formed in all subjects both at baseline and at follow up with the same equipment (EUB-8500 scanner Hitachi Medical Corporation, Tokyo, Japan) and by the same experienced radiologist (Webb M) as described previously^[22,23,25]. The radiologist was blinded to patient allocation and to laboratory values and medical history of the participants. During the ultrasonography, a histogram of brightness levels, *i.e.*, a graphical representation of echo intensity within a region of interest (ROI) was obtained. In the liver, the ROI was measured in the 7th or 8th intercostal space in the mid or anterior axillary line in the superficial aspect of the liver. In the right kidney, the ROI was determined as the cortical area between the pyramids. The brightness level for each organ was recorded and the ratio between the median brightness level of the liver and the right kidney cortex was calculated to determine the HRI. The HRI has been previously demonstrated to be highly reproducible ($r = 0.77$, $P < 0.001$, kappa = 0.86) and was validated against liver biopsy^[26]. $\text{HRI} \geq 1.5$ indicates fatty liver.

Anthropometric and body composition evaluation

Height, weight and waist circumference were measured following a uniform protocol and BMI was calculated. Lean body mass (LBM) and fat mass (FM) were evaluated by the dual energy X-ray absorptiometry (DEXA) method^[27,28] by a blinded technician at the Metabolic Nutrition Clinic.

All participants were instructed to maintain their pre-trial PA habits, regular nutritional intake, medications and nutritional supplements. A weight change during the study of more than 3 kg in either direction, which is clinically significant for NAFLD^[20] and other metabolic parameters^[29,30], was pre-defined as a protocol violation.

Intervention

Patients were randomly allocated either to RT, three times weekly, for 3 mo or a control arm consisting of home stretching.

RT training: The RT program was according to the ACSM 2009 position paper on "Progression Models in Resistance Training for Healthy Adults"^[31]. Exercises included: leg press, leg extension, leg curl, seated chest press, seated rowing, latissimus pull down, biceps curl and shoulder press with 8-12 repetitions, 3 sets for each exercise with 1-2 min rest between sets, for a total duration of about 40 min. Participants performed the training in a community setting in one of the hosting gyms closest to their house or place of work. On the first training meeting, the researchers performed a personal training session and provided explanation on the RT equipment using a comfortable load (determined by volitional fatigue reached with 10-12 repetitions). The load was gradually increased by 2%-10% in the following training sessions, according to the individual ability of the patient (when the patient felt he can perform 1-2 extra repetitions) and with consultation of the profes-

sional trainers of the hosting gym. All changes were routinely documented. Standardization of the RT for all participants was ensured by the highly controlled environment at the gyms and a uniform protocol including: a uniform and meticulous familiarization with the training, all participants (treatment and control) received a comprehensive booklet graphically illustrating by pictures all exercises. Participating gyms (all belonging to a single regional chain) have uniform standard equipment and all the gyms instructors, certified by the sports ministry, were given detailed and comprehensive instructions regarding the training protocol. Using equipment that was not included in the study protocol was not allowed. Every 2 wk phone calls were made to ensure adherence to the training protocol and participants were repeatedly instructed not to perform aerobic training (cycling, treadmill, *etc.*) during the sessions. All patients were observed for an entire exercise session at least twice during the trial by the researchers.

Active control arm: The home stretching routine followed the ACSM's guidelines for a general stretching program^[32]. The program included 8 stretching exercises for the major muscle/tendon groups using the static stretching technique. The participants performed 4 repetitions of these static stretches each lasting 20 s. Each session was performed on 3 non-consecutive days a week^[32]. Participants received a booklet with instructions on the stretching training illustrated by pictures.

Statistical analysis

Statistical analyses were performed using SPSS version 19 (SPSS Inc., Chicago, IL, United States) software and SAS[®] version 9.1 (SAS Institute, Cary North Carolina).

Continuous variables are presented as mean \pm SD. Paired *t*-tests were used to evaluate within group changes from baseline to end of treatment. To test baseline differences in continuous variables between the two groups the independent samples *t*-test was performed. The Wilcoxon signed ranks test or the Mann-Whitney test were used if non-parametric tests were required based on data distribution. Analysis of variance using repeated measurements model was applied for testing the group \times time interactions and exact *F* statistics was performed.

Associations between nominal variables were performed with the Pearson Chi-Square test. Pearson correlation was used to test the correlation between change in HRI and change in other parameters. $P < 0.05$ was considered statistically significant for all analyses.

RESULTS

Trial participants and compliance

Eighty two patients with primary NAFLD were randomized to receive 3 mo of either RT or stretching. Forty four were randomized to the RT group of which 36 (82%) completed the 3 mo follow up period. Thirty eight were randomized to the stretching arm and 33

(87%) completed the study. Two patients dropped out of the RT group due to adverse events (knee pain, shoulder pain), and one from the stretching arm (back pain). Five patients were excluded from analysis because of protocol violation reaching a weight change of more than the pre-defined 3 kg. Hence, thirty three patients in the RT arm and 31 in the stretching arm completed the study per protocol. A flow chart of trial participation is described in Figure 1. The average age was 46.47 ± 10.76 years, with 34 (53%) males. Average BMI was 31.02 ± 4.32 kg/m². The average fasting insulin levels were elevated, but in accordance with the exclusion criteria fasting glucose levels were within the normal range.

All baseline characteristics were similar for the two treatment groups with respect to demographics, anthropometrics and body composition, blood tests including liver enzymes and liver steatosis on imaging as assessed by the HRI (Table 1). Furthermore, no difference in dietary intake at baseline was observed between arms ($P \geq 0.40$ for all comparisons, data not shown).

The average number of training sessions at the gym, that was automatically recorded every time a patient entered the gym with his personal chip, was 2.2 ± 0.65 times a week, representing $73\% \pm 20.5\%$ of the recommended number of sessions of 3 times a week during the 12 wk trial. There was a significant increment in the weight lifted during the trial: leg press increased from 39.73 ± 31.83 to 63.87 ± 44.56 kg ($P < 0.001$), and chest press increased from 20.61 ± 22.34 to 32.09 ± 27.55 kg ($P < 0.001$).

Primary outcome

HRI score was significantly reduced in the RT arm as compared to the stretching arm (-0.25 ± 0.37 vs -0.05 ± 0.28 , $P = 0.017$), representing an 11% vs 3.5% relative reduction from the baseline in the two groups respectively (Figure 2).

The RT arm had a significant but small reduction in weight (-0.39 ± 1.43 kg vs 0.33 ± 1.21 kg) and BMI (Table 2) compared to the stretching arm.

The RT arm had a significant reduction in total FM, trunk fat and android fat and increase in LBM compared to the stretching arm (Figure 3). There was no correlation between the reduction in HRI in the RT arm and weight change or BMI change during the study ($r = 0.25$, $P = 0.17$) nor with total FM change ($r = 0.29$, $P = 0.13$) as observed by DEXA. However, the change in HRI was positively correlated with the change in trunk fat ($r = 0.37$, $P = 0.048$). In contrast, in the stretching arm the change in HRI was positively correlated with weight change ($r = 0.35$, $P = 0.055$) and BMI change ($r = 0.36$, $P = 0.049$).

There was no significant difference between arms in dietary change during the study in total calories, carbohydrates, protein, fat and different types of fat ($P \geq 0.114$ for all comparisons) (Table 2). Furthermore, there was no correlation between the reduction in HRI in the RT arm and change in dietary intake of total calories and different dietary components ($P \geq 0.42$ for all correlations).

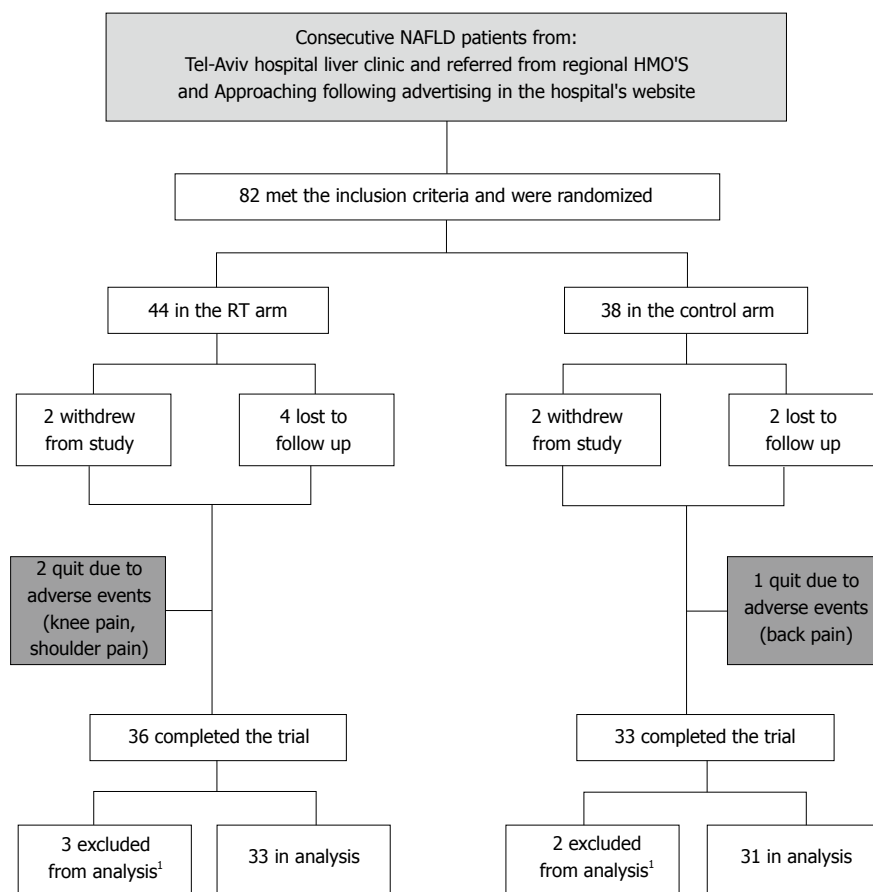


Figure 1 Flow chart of trial participants. ¹Excluded from analysis due to > 3 kg weight change. RT: Resistance training; NAFLD: Non alcoholic liver disease.

Table 1 Comparison between the two treatment arms (mean \pm SD)

Parameter	Normal range	Total population (n = 64)	Resistance training (n = 33)	Stretching (n = 31)	P
Gender (males)		53.1%	48.5%	58.1%	0.443
Age (yr)		46.47 \pm 10.76	46.32 \pm 10.32	46.64 \pm 11.4	0.909
HRI (score)		2.04 \pm 0.45	2.11 \pm 0.44	1.96 \pm 0.46	0.203
BMI (kg/m ²)	20-25	31.02 \pm 4.32	30.75 \pm 4.52	31.30 \pm 4.14	0.617
Waist circumference (cm)		105.85 \pm 10.43	105.05 \pm 10.77	106.71 \pm 10.16	0.527
Systolic BP (mmHg)		120.79 \pm 11.94	119.24 \pm 11.74	122.44 \pm 12.13	0.288
Diastolic BP (mmHg)		76.52 \pm 7.49	75.89 \pm 7.40	77.19 \pm 7.64	0.492
Trunk fat		43.45% \pm 6.21%	44.28% \pm 5.99%	42.55% \pm 6.42%	0.268
Android fat		47.49% \pm 6.41%	48.10% \pm 6.30%	46.88% \pm 6.57%	0.47
Total fat		39.81% \pm 7.89%	40.64% \pm 7.29%	38.92% \pm 8.52%	0.390
Lean body mass		58.20% \pm 7.50%	57.34% \pm 6.89%	59.11% \pm 8.12%	0.349
Physical activity (index)		5.18 \pm 1.84	5.23 \pm 1.80	5.13 \pm 1.92	0.82
Glucose (mg/dL)	70-110	84.44 \pm 9.28	83.82 \pm 8.50	85.10 \pm 10.15	0.586
Insulin (mcu/mL)	5-25	27.40 \pm 10.34	26.75 \pm 9.69	28.10 \pm 11.11	0.605
HOMA (score)		5.80 \pm 2.55	5.65 \pm 2.41	5.97 \pm 2.72	0.616
HbA1C		5.59 \pm 0.47	5.59 \pm 0.49	5.59 \pm 0.46	0.976
Cholesterol (mg/dL)	150-200	186.94 \pm 41.07	192.18 \pm 50.81	181.35 \pm 26.92	0.288
Triglycerides (mg/dL)	50-175	143.80 \pm 66.03	144.88 \pm 75.69	142.65 \pm 55.15	0.894
HDL (mg/dL)		47.51 \pm 11.17	48.32 \pm 12.29	46.65 \pm 9.96	0.553
LDL (mg/dL)		110.72 \pm 33.56	114.94 \pm 40.37	106.23 \pm 24.22	0.296
ALT (U/L)	5-39	51.61 \pm 36.13	53.00 \pm 35.61	50.13 \pm 37.20	0.753
AST (U/L)	5-40	33.19 \pm 16.14	34.30 \pm 17.49	32.00 \pm 14.76	0.572
GGT (U/L)	5-50	50.74 \pm 56.6	55.69 \pm 73.88	45.65 \pm 30.44	0.486
Ferritin (ng/mL)	7.1-151	152.89 \pm 135.81	162.15 \pm 128.24	142.64 \pm 145.39	0.586

HRI: Hepatorenal-ultrasound index; BMI: Body mass index; BP: Blood pressure; HOMA: Homeostasis model assessment; HbA1C: Hemoglobin A1c; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; ALT: Alanine transaminase; AST: Aspartate aminotransferase; GGT: Gamma-glutamyltransferase.

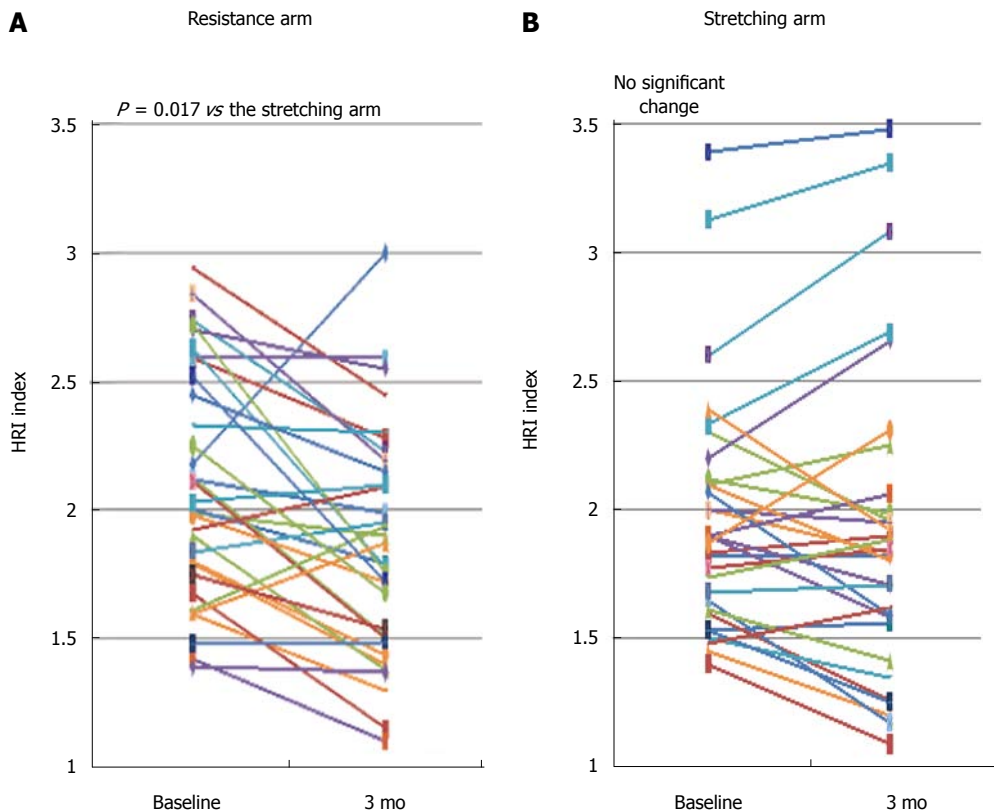


Figure 2 Change (absolute) in hepatorenal-ultrasound index values between baseline and end of trial by treatment arm. A: Resistance arm; B: Stretching arm. Each line represents a single patient. HRI: Hepatorenal-ultrasound index.

Table 2 Between group comparisons of changes from baseline to end of treatment and within group comparisons (mean \pm SD)

Parameter	Normal range	Resistance training ($n = 33$)	Stretching ($n = 31$)	P value between groups
HRI (score)		-0.25 ± 0.37^b	-0.05 ± 0.28	0.017
Weight (kg)		-0.39 ± 1.43	0.33 ± 1.21	0.036
BMI (kg/m^2)	20-25	-0.13 ± 0.49	0.12 ± 0.41	0.036
Waist circumference (cm)		-0.79 ± 2.00^a	0.70 ± 2.62	0.012
Systolic BP (mmHg)		1.27 ± 11.54	-1.19 ± 7.44	0.328
Diastolic BP (mmHg)		-2.53 ± 5.61^a	-0.11 ± 4.43	0.066
Glucose (mg/dL)	70-110	2.24 ± 10.30	-0.23 ± 6.59	0.262
Insulin (mcu/mL)	5-25	0.82 ± 7.04	-0.62 ± 7.97	0.447
HOMA (score)		0.37 ± 2.04	-0.24 ± 1.75	0.209
HbA1C	3.9-6	$-0.01\% \pm 0.13\%$	$0.04\% \pm 0.14\%$	0.186
Cholesterol (mg/dL)	150-200	-8.61 ± 29.2	6.1 ± 17.25	0.018
Triglycerides (mg/dL)	50-175	-13.48 ± 62.30	11.55 ± 51.65	0.086
HDL (mg/dL)		0.13 ± 6.43	0.16 ± 5.64	0.984
LDL (mg/dL)		-6.09 ± 26.38	3.61 ± 14.57	0.076
ALT (U/L)	5-39	-5.30 ± 9.65^b	-5.10 ± 14.43	0.946
AST (U/L)	5-40	-2.76 ± 7.75^a	-2.68 ± 6.95^a	0.965
GGT (U/L)	5-50	-4.25 ± 13.03	2.35 ± 16.48	0.082
Ferritin (ng/mL)		-18.29 ± 48.63^a	8.25 ± 51.09	0.046
Total calories (kcal)		-527.55 ± 786.37^b	-274.29 ± 871.19	0.230
Total fat (g)		-15.09 ± 35.24^b	-5.87 ± 47.82^b	0.386
Carbohydrates (g)		-84.08 ± 121.11^b	-39.38 ± 98.72^a	0.114
Protein (g)		-21.58 ± 41.54^b	-19.30 ± 34.38^b	0.813
Saturated fat (g)		-6.13 ± 10.39^b	-3.07 ± 11.66	0.276
MUFA (g)		-4.00 ± 15.23	-2.44 ± 18.29	0.713
PUFA (g)		-3.45 ± 13.55	0.19 ± 16.64	0.344

For paired samples t -test, $^aP < 0.05$, $^bP < 0.01$ within group comparisons. HRI: Hepatorenal-ultrasound index; BMI: Body mass index; BP: Blood pressure; HOMA: Homeostasis model assessment; HbA1C: Hemoglobin A1c; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; ALT: Alanine transaminase; AST: Aspartate aminotransferase; GGT: Gamma-glutamyltransferase; MUFA: Monounsaturated fat; PUFA: Polyunsaturated fat.

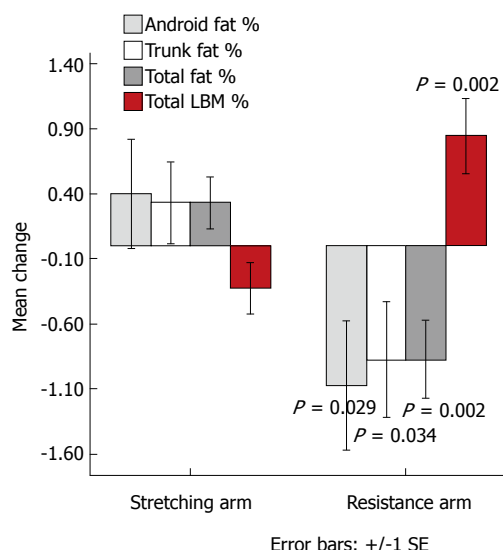


Figure 3 Change (absolute) in body composition parameters between baseline and end of trial by treatment arm. *P* represents the significance of difference between resistance and stretching arm for each parameter ($n = 55$). LBM: Lean body mass.

Secondary outcomes

The RT arm had significantly higher reduction in serum ferritin and total cholesterol. There was no significant difference in reduction of liver enzymes between arms. ALT was significantly reduced only in the RT arm in within group comparison. RT had no significant impact on serum glucose, insulin, glycosylated hemoglobin and triglycerides (Table 2).

DISCUSSION

In this randomized controlled trial, NAFLD patients without diabetes underwent either RT three times weekly or static stretching. The results suggest that RT exerts beneficial effects on several clinical and biochemical parameters including liver fat and body composition.

The 2007 update of the American Heart Association dealing with resistance exercise concludes that RT should be viewed as a complement to aerobic exercise^[14]. However, the beneficial effect of RT for patients with steatosis was so far not supported by strong evidence.

The present trial is one of the first to test this question on a large group of patients. We have demonstrated a significant reduction in steatosis as measured by an objective ultrasonographic tool, the HRI. The modest relative reduction of about 10% is similar to the 13% relative reduction in steatosis previously demonstrated^[7]. Although the RT arm had a nonsignificant reduction in caloric intake and a small but significant weight reduction of less than half a kg, these changes did not correlate with HRI change. Our results suggest that the reduction in steatosis in the RT arm cannot be explained by weight loss or dietary change. RT also improved body composition, most importantly trunk fat mass that was positively correlated with the change in HRI.

The weight-reduction independent beneficial effect

of aerobic exercise in NAFLD is supported by clinical trials demonstrating a relative reduction of hepatic triglyceride concentration by 21%-35%^[33-35] following supervised training such as cycling. However, in a trial of a more modest activity that included brisk walk, there was a relative reduction of 10.3% in liver fat^[36], similar to the one observed by the present study. In previous published trials about the effect of RT in adult NAFLD patients, there was a significant improvement in glycemic control and no improvement in liver enzymes^[7,8]. Our study did not demonstrate improved glucose metabolism, this discrepancy may stem from the exclusion of diabetic patients from our study. It was previously shown that RT improves hyperglycemia, only in patients with disturbed glucose metabolism or diabetes^[37-41]. Our study showed significant improvement in the liver enzymes (ALT and aspartate aminotransferase-AST) within group but with no difference between arms. Interestingly, there seems to be a limited correlation between exercise and liver enzyme reduction. Aerobic PA led to a significant reduction in liver enzymes in some trials^[42] while no reduction was seen in other trials despite reduced steatosis^[8,34,35]. With specific reference for resistance training, it has been shown that weightlifting exercise resulted in increases in liver enzymes; AST and ALT, though the underlying mechanisms are unknown^[43]. Thus, it may be in our study that the reduction of liver enzymes in the RT arm was masked and is underestimated.

Serum ferritin was significantly reduced only in the RT group. This novel effect of RT in NAFLD patients, that has been previously demonstrated with aerobic training^[42] and lifestyle intervention^[44], is of importance due to the strong association of ferritin with fibrosis and inflammation^[45,46] and with insulin resistance (IR)^[23,47] in NAFLD patients. The mechanisms by which PA, and specifically RT, reduces serum ferritin are unknown. Serum ferritin is associated with insulin resistance^[23,48] and is an acute phase protein that can be induced in the setting of systemic or hepatic inflammation^[49-52]. Serum ferritin was demonstrated to be a predictor of histologic severity including steatosis^[46]. Thus, we can assume that a reduction in liver fat demonstrated in our study or improved hepatic insulin sensitivity by RT, that was demonstrated in another study^[6], led to a reduction of serum ferritin. Furthermore, RT may have an anti-inflammatory effect, as demonstrated by increasing adiponectin levels^[53], and serum ferritin was found to be inversely correlated with serum adiponectin^[54]. However, it is unclear if hyperferritinemia in NAFLD is simply a consequence of disease severity or actively contributes to disease progression^[46]. Ferritin was found to inhibit the secretion of apolipoprotein B and in this way may alter cholesterol and triglyceride transport in the liver^[55]. Interestingly, some studies reported that PA plays an important role in reducing serum ferritin concentration^[56,57] and this may be another explanation for the reduction in liver fat in our study.

Another beneficial effect of RT in our study was a significant reduction of serum cholesterol. Although data regarding the effect of RT on lipid metabolism are

equivocal, reduction of serum total cholesterol and LDL by resistance training has been previously demonstrated in a meta-analysis of randomized controlled trials^[58]. It is well established that liver steatosis is associated with IR and lipid abnormalities including alteration in cholesterol metabolism^[59-62]. Recent data show that increased IR contributes to the shift in cholesterol metabolism to increased synthesis and decreased absorption, independent of body weight^[63-65]. Several studies have demonstrated that resistance training improves IR, including hepatic IR^[6,66], and therefore may contribute to decreased synthesis of hepatic cholesterol. However, the precise mechanisms involved still need to be clarified^[67].

Professional societies recommend ≥ 30 min of moderate-intensity aerobic PA on most, and preferably all, days of the week, or vigorous-intensity PA ≥ 3 times per week for ≥ 20 min each time. However, only 27.7% United States adults meet recommended levels of either moderate or vigorous physical activity, whereas 29.2% report no regular PA outside of their work^[68,69]. Moreover, the prevalence of physically active adults among patients with diabetes is lower than in those without diabetes^[70] and they are less likely to meet PA recommendations^[71]. In NAFLD patients, compliance may be even lower because fatigue has been demonstrated to be markedly higher in NAFLD patients compared to controls, and is associated with inactivity and excessive daytime sleepiness^[10]. Therefore, an alternative or a complement form of exercise that may be easier to perform or to adhere to, such as RT, may be helpful in the treatment of NAFLD patients.

The major limitation of this study is that due to ethical and practical considerations we were unable to perform repeated liver biopsies in our short term study preventing any inference regarding the effect of RT on inflammation and fibrosis. Ideally, quantification of liver fat is performed by liver biopsy or magnetic resonance spectroscopy (¹H-MRS) that is an accepted noninvasive method to reliably quantify steatosis^[72,73].

HRI has been validated *vs* liver biopsy and provides a highly sensitive, objective and quantitative tool for liver fat evaluation with a high correlation ($r = 0.82$, $P < 0.001$) and a kappa of 0.75 as compared with histological steatosis^[26]. Another group compared HRI to ¹H-MRS as a reference standard, demonstrating high correlation ($r^2 = 0.92$, $P < 0.0001$) and therefore confirming that HRI can be a valuable analytic tool in clinical investigation^[72]. It was also recently shown that HRI highly correlates with biochemical surrogate markers of liver steatosis: the fatty liver index (FLI) ($r = 0.55$, $P < 0.001$) and the SteatoTest ($r = 0.52$, $P < 0.001$)^[74]. Furthermore, since a baseline biopsy wasn't performed, we were unable to distinguish between patients with simple steatosis or NASH. NASH is the NAFLD variant that needs to be treated more urgently due to a worse natural history of progression to cirrhosis, hepatocellular carcinoma^[75] and increased liver related mortality^[76]. Recently, ultrasonographic FLI, another semi-quantitative evaluation tool of hepatic ste-

atosis, was demonstrated to successfully predict biopsy diagnosed NASH^[77].

In conclusion, this relatively large randomized clinical trial demonstrated a significant reduction in steatosis, as assessed by HRI, during 3 mo RT accompanied by favorable changes in body composition and reduction of serum ferritin.

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COMMENTS

Background

Lifestyle modifications, including weight reduction and physical activity, improve many of the risk factors for non alcoholic liver disease (NAFLD) and have become the primary treatment modalities for the disease. The role of physical activity as a potential treatment for NAFLD has been tested in several observational studies and a few clinical trials, mostly testing the effect of aerobic training.

Research frontiers

Resistance training (RT) (strength training) is a means for developing and maintaining muscular strength, endurance, power, and muscle mass that has grown in popularity over the past two decades. In a study of the general population, resistance training was inversely associated with NAFLD. This association remained significant after adjusting to multiple confounders including body mass index, homeostasis model assessment, nutritional factors, adiponectin, and resistin. Small trials found beneficial effects for RT as a single treatment in NAFLD patients, but results regarding reduction in steatosis were conflicting.

Innovations and breakthroughs

Aerobic training is a recommended treatment for NAFLD. Resistance training is viewed as a complement to aerobic training. However, data on the effect of resistance training on NAFLD is scant. In this study, three months of resistance training in NAFLD patients exerted reduction in liver fat as well as reduction in total body and trunk fat with increase in lean body mass. Furthermore, resistance training led to reduction in serum ferritin.

Applications

In NAFLD patients, compliance to aerobic training may be low due to fatigue. Therefore, resistance training can serve as an easier alternative or a complement form of exercise in these patients.

Terminology

Hepato-renal index (HRI): During the ultrasonography, a histogram of brightness levels, *i.e.*, a graphical representation of echo intensity within a region of interest (ROI) is obtained in the liver and in the right kidney. The brightness level for each organ is recorded and the ratio between the median brightness level of the liver and the right kidney cortex is calculated to determine the HRI. Resistance training (strength training) is a means for developing and maintaining muscular strength, endurance, power, and muscle mass.

Peer review

The study is an independent study focusing on the physical exercise pattern and the improvement of vital parameters in NAFLD patients. The study demonstrates an important aspect of resistance training that can be added to the therapeutic approach benefiting patients with NAFLD. This randomized trial is of potential interest given the paucity of data on effective NAFLD treatment.

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