Moderate-Intensity Aerobic vs Resistance Exercise and Dietary Modification in Patients With Nonalcoholic Fatty Liver Disease: A Randomized Clinical Trial

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INTRODUCTION: **This randomized trial aimed to compare the effects of moderate-intensity aerobic vs resistance exercise with dietary modification in patients with nonalcoholic fatty liver disease (NAFLD).**

METHODS: **Patients with NAFLD were randomly assigned (1:1) to a 12-week supervised training program of moderate-intensity aerobic or resistance exercise with dietary intervention consisting of monthly individual nutritional counseling by a dietician. Transient elastography, anthropometry, body composition, cardiorespiratory fitness, biochemistries, and glucose tolerance were measured at baseline and 12 weeks.**

RESULTS: **Eighteen subjects exercised for an average of 3.35 ± 0.30 sessions a week in the aerobic group, and 17 subjects exercised an average of 3.39 ± 0.28 sessions a week in the resistance group. After completion of the training program, hepatic fat content was similarly reduced in both groups ($P < 0.001$). The mean relative reduction from baseline in the aerobic group was -10.3% (95% confidence interval -18.2 to -2.40) and the resistance group was -12.6% (-20.5 to -4.69). Liver steatosis (defined as controlled attenuation parameter >248 dB/m) disappeared in 9 (50%) of the aerobic group and in 9 (53%) of the resistance group. Whole-body and muscle insulin sensitivity indexes were improved, and waist circumference was reduced comparably in both exercise groups. The number of exercise sessions per week was correlated with the absolute reduction in hepatic fat content ($r = 0.52$; $P = 0.001$). Weekly exercise training ≥3 sessions substantially attenuates liver fat accumulation independent of weight loss.**

DISCUSSION: **Moderate-intensity aerobic training and resistance training with dietary modification are equally effective for reducing intrahepatic fat and improving underlying insulin resistance among patients with NAFLD.**

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is recognized as the most prevalent cause of chronic liver disease worldwide. Currently, there is no approved pharmacotherapy for NAFLD. Lifestyle intervention involving dietary changes and regular exercise is the cornerstone of managing patients with NAFLD (1,2). However, the current recommendations do not specify what exercise regimen is most beneficial, and the mechanisms by which exercise affects the liver remain unclear.

A recent systematic review of randomized controlled trials of moderate-intensity aerobic exercise showed that hepatic steatosis assessed by imaging improved after 4–32 weeks of exercise training for 3–5 days a week, independent of weight loss (3). Similarly, an improvement in hepatic steatosis was observed in randomized controlled trials of resistance exercise 3 days a week over 8–12 weeks (3). These findings suggest that both aerobic exercise and resistance exercise effectively reduce hepatic steatosis in patients with NAFLD. However, Slentz et al. (4) found that aerobic exercise is more effective than resistance exercise for reducing intrahepatic lipid, while Bacchi et al. (5) and Shamsoddini et al. (6) demonstrated that both types were equally effective. Because both forms of exercise have different

characteristics, we, therefore, conducted a head-to-head comparison between moderate-intensity aerobic and resistance exercise for patients with NAFLD.

METHODS

Study population

A randomized trial (Clinical Trials NCT02679417) was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board. All study participants were medical personnel who were recruited using flyers and posters placed on campus. Sedentary individuals with the absence of significant alcohol consumption (alcohol intake <20 g/d for women or <30 g/d for men) were invited to attend an ultrasonographic examination. Subjects who had bright liver on ultrasonography were asked to confirm a diagnosis of liver steatosis with transient elastography using the controlled attenuation parameter (CAP) >248 dB/m (7). Subjects were excluded if they had evidence of viral hepatitis, autoimmune liver disease, hemochromatosis, or drug-induced hepatotoxicity; they were engaging in weight loss program or structured physical activity for the previous 3 months; they had medical conditions preventing participation in the exercise program; or used drugs known to influence glucose metabolism and body composition.

Nutritional counseling

After enrollment, all participants were asked to adopt the nutritional counseling offered by an experienced dietician for modifying their dietary habits during a 4-week run-in period. The purpose of this was to identify individuals who might dropout before initiation of exercise training and increase compliance with the recommended nutrition throughout the study. Thereafter, participants underwent monthly nutritional counseling by the same dietician during a 12-week exercise period. The goal of nutritional counseling was to induce a negative calorie balance in overweight/obese subjects and allow a neutral calorie balance in normal-weight subjects. At each visit, subjects were asked to fill out a 3-day food diary to assess adherence to dietary intervention.

Exercise intervention

After the run-in period, qualified subjects were randomly assigned to aerobic exercise or resistance exercise plus dietary modification for 12 weeks with an allocation ratio of 1:1. The randomization schedules were generated using nQuery statistical software (Statsols, San Diego, CA) and concealed until an eligible participant was ready for the exercise intervention.

All subjects were scheduled for exercise training 5 times per week over 12 weeks at the institute's fitness center. The exercise sessions were supervised by accredited exercise specialists and were documented to ensure adherence during the study. The aerobic exercise program required participants to exercise for 60 minutes per session with treadmills, ellipticals, or stationary bikes with progressively increased duration and intensity. Aerobic exercise consisted of 3 phases: warm-up, training, and cool down. At baseline, the training phase commenced with two, 15-minute running periods on a treadmill at 60% of their maximal heart rate during the first week and then increased to 2, 15-minute running periods at 70% maximal heart rate during weeks 2–12.

The resistance program included a series of 10 whole-body exercises for 60 minutes per session. Each training session included leg press, leg extension, leg flexion, chest press, latissimus pull-down, seated row, biceps curl, and triceps extension with stack weight equipment. In addition, a single set of push-ups and sit-ups was performed. For the first 4 weeks, participants performed 1 or 2 sets of 8–12 repetitions at 60% of their 1 repetition maximum with proper lifting techniques. During weeks 5–12, subjects completed 2 sets of 8–12 repetitions at 60% of their 1 repetition maximum to fatigue. Subjects took 1–2 minutes of rest between exercise sets.

Hepatic fat content and liver stiffness

Transient elastography was performed by a single experienced operator blinded to group allocation using FibroScan (Echosens, Paris, France) with the M probe to measure liver stiffness and quantification of hepatic fat content using a software device denominated CAP. The median values of the successful liver stiffness and CAP measurements were expressed in kilopascals and decibels per meter, respectively.

Body composition and cardiorespiratory fitness

Weight and height were measured using standard procedures. Body composition parameters were measured using the multifrequency bioelectrical impedance analyzer (TANITA BC-418; Tanita, Tokyo, Japan).

Participants performed the Åstrand-Rhyming submaximal exercise test on a stationary bicycle at baseline and after 12 weeks of exercise. The maximal volume of oxygen consumption (VO_{2max}) was estimated by applying the work rate and mean heart rate of the fifth and sixth minute to the Åstrand nomogram, with correction for weight and age.

Biochemistry analyses

At baseline and after 12 weeks of exercise, blood samples after overnight fasting were obtained to measure total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, ferritin, uric acids, and high-sensitivity C-reactive protein level. The oral glucose tolerance test (75-g dextrose monohydrate in 250-mL water) with 0-, 30-, 60-, 90-, and 120-minute sampling to determine plasma glucose and insulin concentrations was performed at baseline and 12 weeks. A number of indexes related to insulin resistance, insulin secretion, and β-cell function were calculated using the validated methods (8–12).

Statistical analysis

The primary outcome was a change in hepatic fat content quantified by CAP after the 12-week exercise training. The 12 weeks of moderate-intensity aerobic exercise has reported a 20%–23% relative reduction in liver fat (13,14). Resistance training for 8–16 weeks produced a 13%–26% relative reduction in liver fat (5,15). Based on these reported efficacies, we expected the aerobic group to have a 23% relative reduction in liver fat and the resistance group to have a 15% relative reduction in liver fat after the 12-week training program. We need a minimum sample size of 18 patients in each arm to achieve 80% power for detecting the difference at a 5% significance level. Allowing an attrition rate of 5%, a total sample size of 38 patients was required.

Data were summarized using descriptive statistics. Repeated-measures ANOVA was performed to compare changes over the 12 weeks of intervention, with the outcomes assessed in the study as the dependent variable and time, study group, and time-by-

group interaction as the independent variables. Relative changes from baseline were compared in both intervention groups by the Mann-Whitney test. The relationships between variables of interest were evaluated with Spearman rank correlation analysis. Multiple linear regression analysis was performed to determine factors associated with changes in hepatic fat content. The data were analyzed using a modified intention-to-treat approach for subjects who completed the study. Statistical significance was set at a P value of less than 0.05. The SPSS software package version 18.0 (SPSS, Chicago, IL) was used to analyze the data.

RESULTS

Patient characteristics

We screened 105 individuals, of whom 38 subjects with NAFLD were eligible and randomly assigned to either aerobic exercise (n = 19) or resistance exercise (n = 19) training (Figure 1). One patient assigned to aerobic training, and 2 patients assigned to resistance training withdrew before starting the exercise intervention. The final analysis was performed on 18 subjects in the aerobic group and 17 subjects in the resistance group.

The 2 groups were similar in baseline clinical characteristics and metabolic profiles (Table 1). No participants received insulin-sensitizing or lipid-lowering drugs. Thirty-five subjects completed the exercise program. On average, subjects completed 3.35 ± 0.30 exercise sessions per week in the aerobic group and 3.39 ± 0.28 sessions per week in the resistance group. During the 12-week intervention, daily calorie intakes and macronutrients remained unchanged from baseline and did not differ significantly between the groups.

Hepatic fat content and liver stiffness

Both exercise regimens elicited a significant and comparable reduction in liver fat content (Figure 2a). The mean relative reduction from baseline was −10.3% (95% confidence interval −18.2 to −2.40) in the aerobic group and −12.6% (−20.5 to −4.69) in the resistance group (Figure 2b). The relative decrease in liver fat content did not correlate with body weight change after 12 weeks of exercise ($P = 0.190$). At the end of the exercise training, hepatic steatosis (defined as CAP >248 dB/m) was no longer present in 9 of 18 subjects (50%) in the aerobic group and in 9 of 17 subjects (53%) in the resistance group ($P = 0.862$) (Figure 2c). The magnitude of the changes in liver stiffness was not different from baseline to week 12 ($P = 0.733$) or by a group-by-time interaction analysis ($P = 0.967$).

Body composition and cardiorespiratory fitness

Both exercise regimens produced a similar reduction in body weight. The aerobic group had a mean relative reduction in body weight from baseline of −4.8% (95% confidence interval −7.4 to −2.1) and the resistance group was −4.2% (−6.9 to −1.5). Waist circumference significantly reduced in both groups. Changes in body mass index, body fat mass, and skeletal muscle mass during 12 weeks were not statistically different (Table 2). Cardiorespiratory fitness (VO_{2max}) increased after aerobic and resistance exercise training ($P = 0.001$) but did not significantly differ between both groups.

Insulin resistance indexes

Both aerobic and resistance groups had significantly improved the homeostatic model assessment of insulin resistance (HOMA-IR), the muscle insulin sensitivity index (MISI), and the homeostasis model assessment of beta-cell function (HOMA-B) from baseline to week 12 ($P < 0.05$) (Table 3). Group-by-time
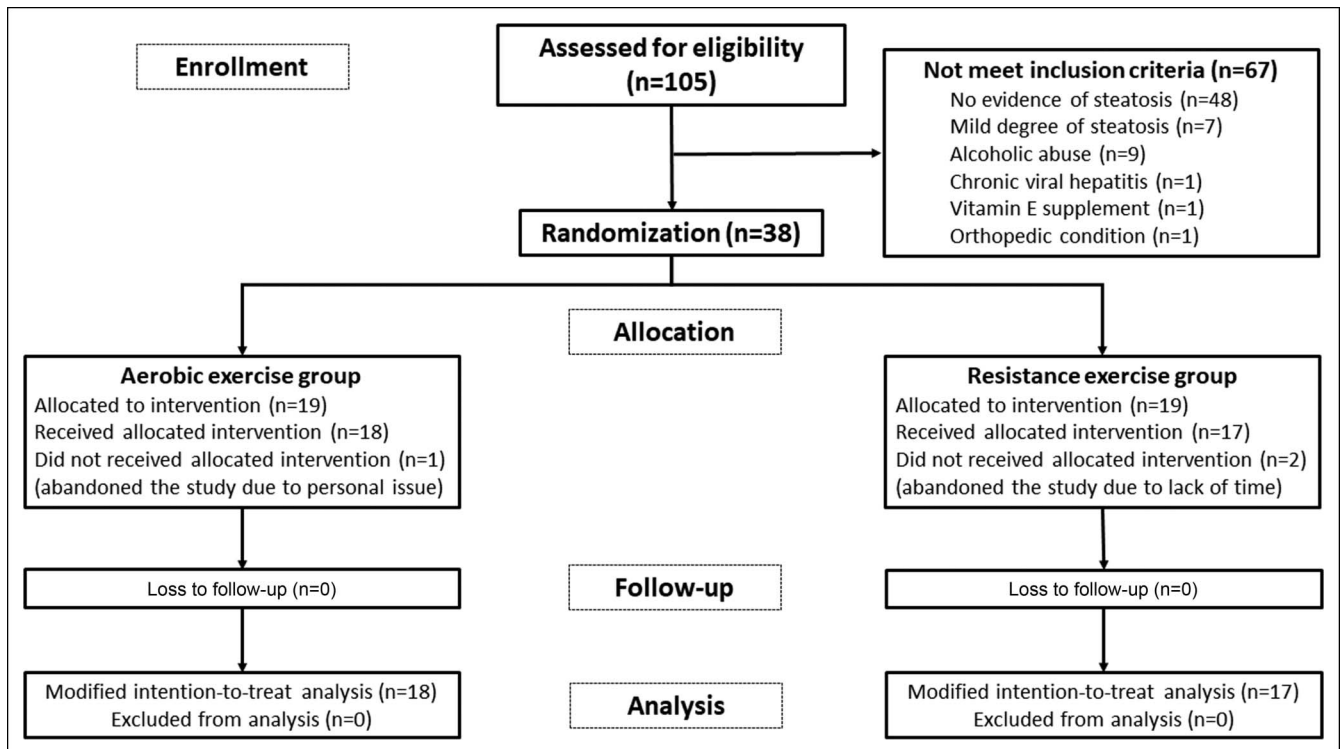

Figure 1. Flow diagram of the trial.

LIVER

Table 1. Baseline characteristics of enrolled subjects

	Aerobic exercise (n = 18)	Resistance exercise (n = 17)
Age, yr	37.4 ± 1.9	38.2 ± 2.2
Men/women, n/n	5/13	3/14
Body weight, kg	70.6 ± 2.4	70.8 ± 4.2
Waist circumference, cm	86.6 ± 1.6	88.3 ± 2.4
Waist-to-hip ratio	0.87 ± 0.01	0.90 ± 0.01
Body mass index, kg/m^2	26.8 ± 0.7	27.3 ± 0.9
Body fat mass, kg	23.3 ± 1.3	25.7 ± 2.0
Visceral fat rating	8.59 ± 0.70	8.65 ± 0.84
Skeletal muscle mass, kg	44.5 ± 2.1	44.6 ± 2.9
Systolic blood pressure, mm Hg	129 ± 3.8	127 ± 2.7
Diastolic blood pressure, mm Hg	86 ± 2.6	82 ± 2.5
Fasting plasma glucose, mg/dL	89.9 ± 2.0	93.1 ± 3.7
Total cholesterol, mg/dL	212.6 ± 5.2	206.8 ± 9.1
Triglyceride, mg/dL	141.2 ± 19.5	146.1 ± 31.7
HDL-C, mg/dL	55.5 ± 4.2	55.9 ± 3.6
LDL-C, mg/dL	128.8 ± 5.7	124.8 ± 8.5
AST, U/L	22.4 ± 2.1	19.9 ± 2.5
ALT, U/L	31.6 ± 7.8	17.6 ± 2.3
GGT, U/L	48.1 ± 10.5	36.3 ± 8.5
Uric acid, mg/dL	5.6 ± 0.3	5.0 ± 0.4
Ferritin, ng/dL	148.2 ± 29.5	150.4 ± 32.9
C-reactive protein	2.3 ± 0.6	4.1 ± 0.7
Controlled attenuation parameter, dB/m	284.2 ± 8.3	296.1 ± 9.1
Liver stiffness, kPa	4.5 ± 0.2	4.3 ± 0.2
Total caloric intake, kcal/d	1,122 ± 71	1,148 ± 89
Fat (% intake)	32.6 ± 1.7	32.9 ± 1.1
Carbohydrate (% intake)	50.9 ± 2.2	47.9 ± 1.2
Protein (% intake)	16.5 ± 1.0	19.2 ± 1.1

Data are described as the number with percentage for categorical variables and as mean ± SE of the mean for continuous variables.

ALT, alanine aminotransferase; AST aspartate aminotransferase; GGT, gamma-glutamyl transferase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

interaction analysis revealed no significant differences in the magnitude of changes in HOMA-IR, MISI, and HOMA-B. There were no significant differences between groups on Matsuda insulin sensitivity index, hepatic insulin resistance index, disposition index, and insulinogenic index.

Metabolic parameters and liver enzymes
Exercise training did not affect plasma glucose, total cholesterol, triglyceride, high-density lipoprotein cholesterol, or low-density lipoprotein cholesterol concentrations (Table 3). The magnitude of change in serum concentrations of aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, uric acid,

ferritin, and high-sensitivity C-reactive protein from baseline to the end of the intervention was not significantly different.

### Factors associated with the change in hepatic fat content
The correlation analyses were performed using combined data from all participants because there were no significant differences between the groups. In univariate correlation analysis, the absolute reduction in hepatic fat content after training was positively associated with changes in body weight ($r = 0.51$; $P = 0.002$), waist circumference ($r = 0.48$; $P = 0.004$), body fat mass ($r = 0.52$; $P = 0.001$), visceral fat rating ($r = 0.61$; $P < 0.001$), and muscle mass ($r = 0.42$; $P = 0.012$), but inversely associated with changes in the MISI ($r = -0.45$; $P = 0.007$). The number of exercise sessions per week was significantly associated with the absolute reduction in hepatic fat content ($r = 0.52$; $P = 0.001$). Changes in VO$_{2max}$ ($P = 0.128$), HOMA-IR ($P = 0.821$), Matsuda index ($P = 0.301$), hepatic insulin resistance index ($P = 0.660$), disposition index ($P = 0.990$), HOMA-B ($P = 0.577$), or insulinogenic index ($P = 0.781$) were not associated with changes in hepatic fat content. In the multivariate regression analysis, adjusting for age and sex, improvement in hepatic fat content after 12 weeks of the exercise was significantly associated with increasing numbers of weekly exercise sessions and improvement in MISI (R^2 model $= 0.54$, $P = 0.004$).

We further investigated the effects of training frequency on changes in hepatic fat content and other variables. The data were reanalyzed to compare subjects who participated for ≥3 times weekly of the scheduled exercise sessions (n = 21) to those who participated <3 times weekly (n = 14). The mean reductions in hepatic fat content, weight, and body fat mass were significantly greater in patients training ≥3 times weekly compared with those training <3 times weekly (Figure 3a–c). A comparison between the weekly training ≥3 and <3 times groups adjusted for changes in weight revealed greater improvements in hepatic fat content in subjects who exercised ≥3 times weekly group ($P = 0.01$). At the end of the exercise training, hepatic steatosis (defined as CAP >248 dB/m) was no longer present in 15 of 21 subjects (71%) who exercised ≥3 times weekly and in 3 of 14 subjects (21%) who exercised <3 times weekly ($P = 0.004$) (Figure 3d).

DISCUSSION
Although exercise is generally beneficial, the optimal regimen of exercise has relevance for subjects with NAFLD. Several studies have addressed the issue of the optimal exercise prescription, and a few randomized controlled trials have compared the effects of aerobic vs resistance exercise for patients with NAFLD (4–6). It is difficult to establish the effect of exercise *per se* in 1 trial focused on type 2 diabetic patients with NAFLD (5), as some cases had been treated with insulin-sensitizing agents that potentially improve steatosis. By contrast, a larger trial found that aerobic exercise was more effective than resistance exercise for reducing liver fat (4). However, the study design compared resistance exercise with a more substantial intensity aerobic training and thus cannot exclude that similar intensity aerobic and resistance exercise might be equally effective.

We observed that both 12-week resistance training and aerobic training reduced hepatic fat content in subjects with NAFLD, independent of weight loss. Both supervised exercise programs resulted in significant improvements in whole-body and muscle insulin sensitivity and a modest reduction in visceral adiposity.
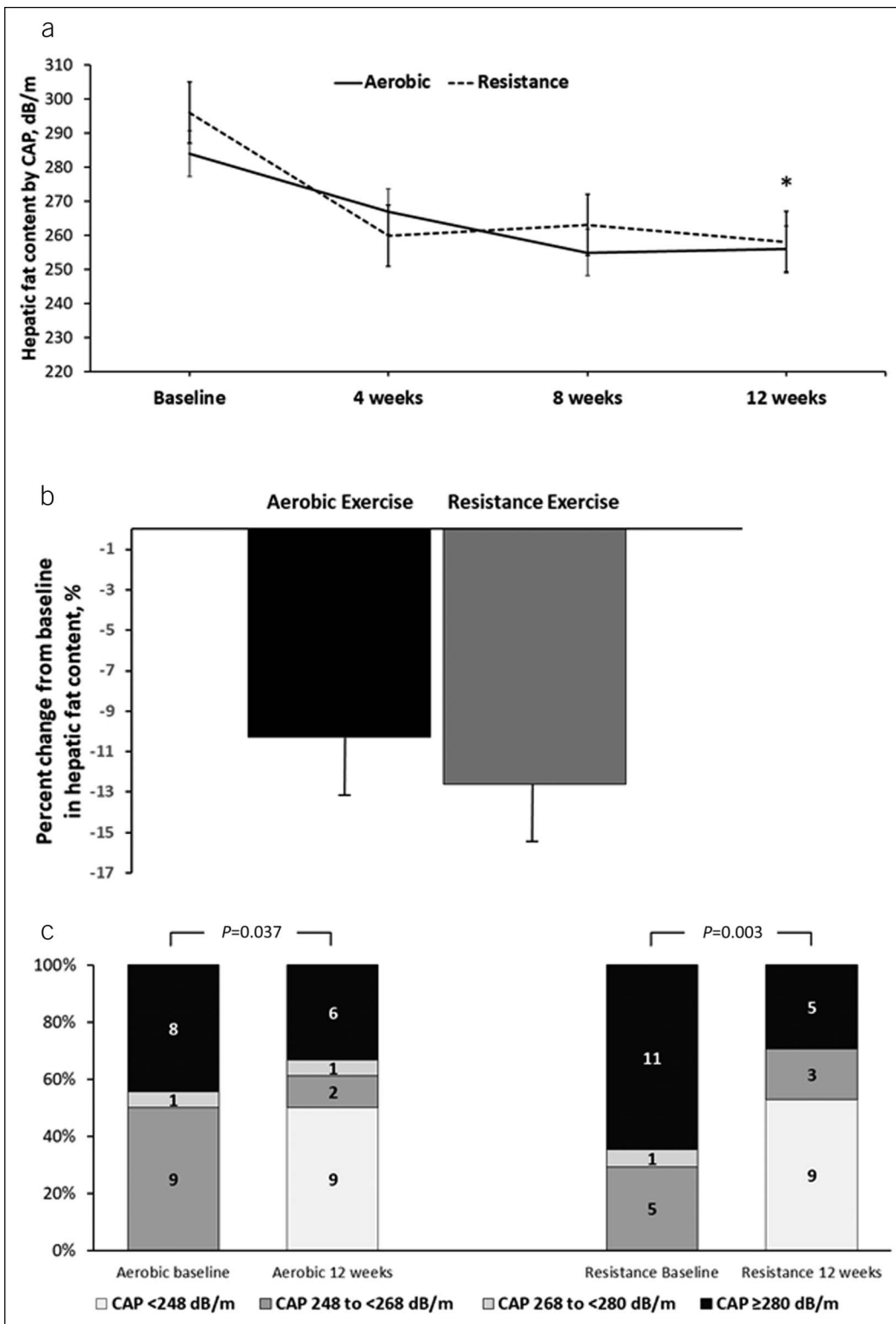
Figure 2. Absolute and relative reductions in hepatic fat content after 12 weeks of either aerobic or resistance exercise. Data are mean and SE of the mean. (**a**) Absolute values in hepatic fat content before and after exercise. (**b**) Percent changes in hepatic fat content after exercise. (**c**) Severity of hepatic steatosis before and after exercise. *Significant time effect by repeated-measures ANOVA ($P = 0.020$), with no significant interaction by group. Percent changes were not significantly different between the 2 groups (by the Mann-Whitney test). CAP, controlled attenuation parameter.

LIVER

Table 2. Body composition and cardiorespiratory fitness observed after 12 weeks of aerobic and resistance exercise

	Aerobic exercise	Resistance exercise	P value time	P value time-by-group interaction
Body weight, kg	−3.75 (−5.81 to −1.69)	−3.58 (−6.65 to −0.51)	0.839	1.000
Waist circumference, cm	−6.76 (−9.74 to −3.79)	−6.59 (−9.14 to −4.04)	0.006	0.996
Waist-to-hip ratio	−0.01 (−0.03 to 0.01)	−0.02 (−0.04 to 0.01)	0.520	0.950
Body mass index, kg/m^2	−1.46 (−2.29 to −0.64)	−1.24 (−2.19 to −0.29)	0.637	0.981
Body fat mass, kg	−2.70 (−4.25 to −1.15)	−2.96 (−5.42 to −0.51)	0.548	0.993
Visceral fat rating	−0.71 (−1.21 to −0.20)	−0.88 (−1.54 to −0.23)	0.828	0.998
Fat free mass, kg	−1.05 (−1.70 to −0.39)	−1.20 (−2.23 to −0.17)	0.992	1.000
Skeletal muscle mass, kg	−0.98 (−1.60 to −0.36)	−2.71 (−6.13 to 0.70)	0.935	0.996
VO$_{2max}$, mL/kg/min	6.46 (2.89–10.0)	5.57 (2.76–8.37)	0.001	0.789

Data are mean (95% confidence interval). *P* values refer to comparisons between groups by repeated-measures ANOVA.
VO$_{2max}$, the maximal volume of oxygen consumption.

Thus, resistance exercise may be more feasible for patients with NAFLD who cannot participate in aerobic fitness because of poor cardiorespiratory endurance or body habitus. We did not observe significant changes in liver fibrosis in our subjects despite a clear improvement in hepatic fat content. It can be explained by the fact that all subjects had no or mild fibrosis at enrollment.

Excess liver and visceral adipose tissue are known to be independently associated with the cardiometabolic risk in obesity (16,17). Lifestyle modification through exercise training programs reduces liver fat and visceral adiposity, even in the absence of weight loss (5,18,19). Our results extend this by demonstrating that both aerobic exercise and resistance exercise reduce liver fat and visceral adiposity, and the benefits can be enhanced by increasing the weekly frequency of exercise. Furthermore, it is essential to establish whether a minimum threshold for exercise benefit exists given the barriers to adopting structured exercise

Table 3. Insulin indexes and metabolic changes observed after 12 weeks of aerobic and resistance exercise

	Aerobic exercise	Resistance exercise	P value time	P value time-by-group interaction
HOMA-IR	−1.21 (−2.35 to −0.08)	−0.61 (−1.34 to 0.13)	0.046	0.502
ISI Matsuda	5.40 (0.83–9.97)	1.25 (−3.45 to 5.96)	0.062	0.241
HIRI	−34.4 (−75.5 to 6.57)	−1.56 (−26.3 to 23.1)	0.185	0.224
MISI	4.48 (−2.71 to 11.7)	6.92 (−0.36 to 14.2)	0.037	0.220
Disposition index	1.83 (−1.41 to 5.09)	6.64 (−1.73 to 15.0)	0.089	0.331
HOMA-B	−1.21 (−2.35 to −0.08)	−0.61 (−1.34 to 0.13)	0.043	0.397
Insulinogenic index	−0.53 (−1.29 to 0.22)	0.65 (−0.25 to 1.56)	0.846	0.068
Glucose, mg/dL	−1.44 (−4.59 to 1.70)	−2.76 (−6.37 to 0.84)	0.287	0.905
Total cholesterol, mg/dL	−7.39 (−23.4 to 8.62)	−7.82 (−19.0 to 3.34)	0.181	0.884
LDL-C, mg/dL	−0.36 (−10.3 to 9.55)	−0.60 (−13.7 to 12.5)	0.562	0.879
HDL-C, mg/dL	−2.33 (−7.36 to 2.69)	−1.71 (−5.65 to 2.24)	0.578	0.925
Triglycerides, mg/dL	−23.5 (−66.4 to 19.4)	−43.2 (−87.8 to 1.49)	0.203	0.728
AST, U/L	4.39 (−0.70 to 9.48)	−0.76 (−4.37 to 2.84)	0.797	0.589
ALT, U/L	0.94 (−8.45 to 10.3)	−0.29 (−5.44 to 4.85)	0.999	0.950
GGT, U/L	−9.14 (−27.3 to 8.99)	−4.62 (−18.0 to 8.73)	0.972	0.897
Uric acid, mg/dL	−0.14 (−0.59 to 0.32)	0.18 (−0.33 to 0.68)	0.960	0.673
Ferritin, ng/dL	−25.5 (−46.9 to −4.13)	−27.1 (−58.7 to 4.46)	0.391	0.979
C-reactive protein	0.50 (−0.39 to 1.39)	0.61 (−2.30 to 3.52)	0.515	0.924

Data are mean (95% confidence interval).
ALT, alanine aminotransferase; AST aspartate aminotransferase; GGT, gamma-glutamyl transferase; HDL-C, high-density lipoprotein cholesterol; HIRI, hepatic insulin sensitivity index; HOMA-B, homeostatic model assessment of β-cell function; HOMA-IR, homeostatic model assessment of insulin resistance; ISI, insulin sensitivity index; LDL-C, low-density lipoprotein cholesterol; MISI, muscle insulin sensitivity index.
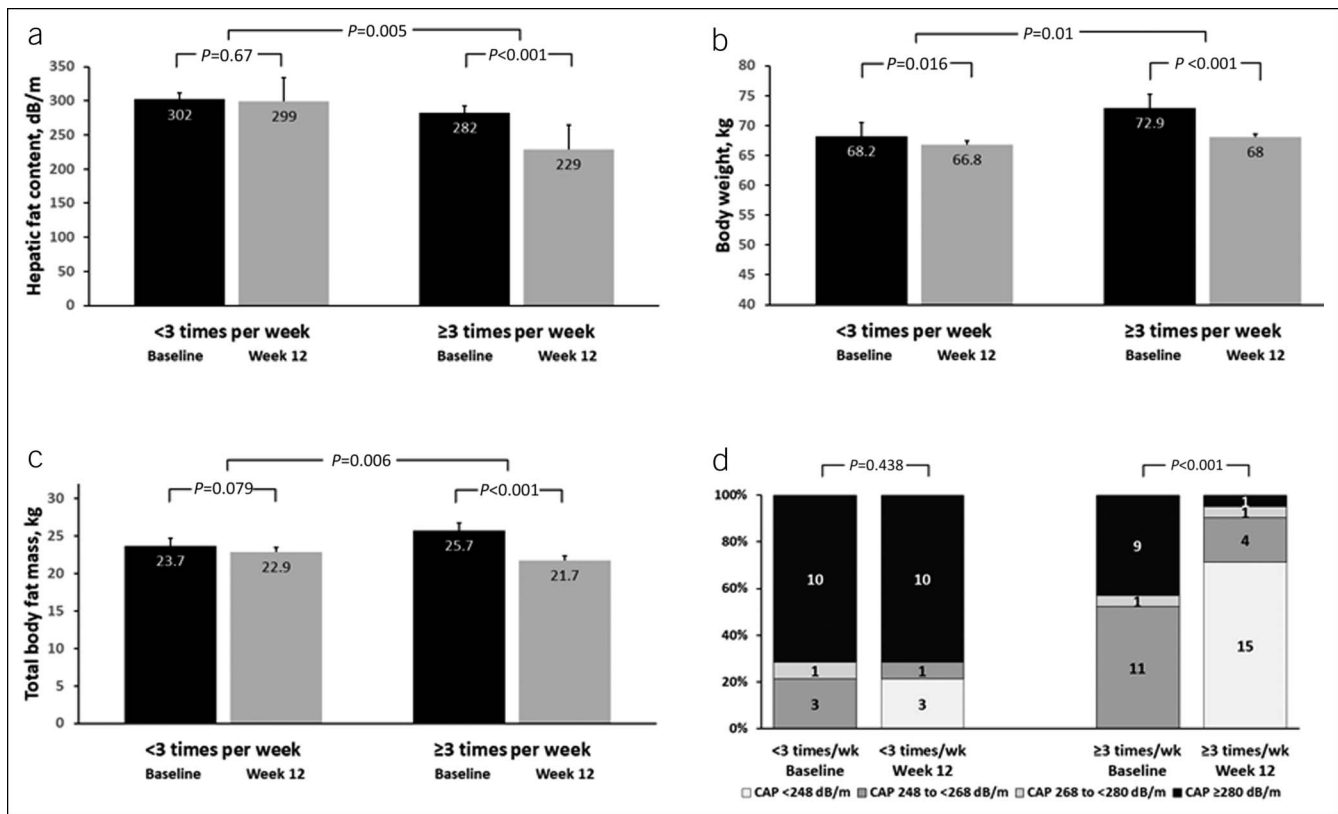
Figure 3. Hepatic fat content (**a**), body weight (**b**), total body fat mass (**c**), and severity of hepatic steatosis (**d**) before and after intervention in the groups of patients who exercised <3 and ≥3 times per week. CAP, controlled attenuation parameter.

programs. Our analysis demonstrates that exercise at least 3 times a week yielded highly significant improvements and resolution of hepatic steatosis after a short-term training program. Our regression model adjusted for change in weight during the training period and revealed an increasing strength of association between improved hepatic fat content and increasing frequency of exercise. Furthermore, a dose-response relationship was observed between exercise frequency and NAFLD resolution, suggesting a true causal relationship. These results support the current public health recommendations for patients with NAFLD to participate in moderate-intensity exercise at least 3 sessions a week. However, we acknowledge that our results are specifically applicable to adults with NAFLD and no/minimal fibrosis. Further research is needed to explore the effects of exercise among patients with significant liver fibrosis.

Recent research has focused on the effects of different intensities of exercise in patients with NAFLD. Several trials demonstrated that the effect of moderate-intensity exercise on hepatic fat content varied from 0.8% to 21% relative reduction, and the average weight loss varied from 0.1% to 7.2% of initial body weight (4–6,18). These findings are in line with our results, showing that moderate-intensity exercise training significantly reduces hepatic fat content by 10.3%–12.6% in subjects with NAFLD despite minimal changes in weight. We also found significant improvement in cardiorespiratory fitness for moderate-intensity resistance exercise, similar to that for the aerobic training program. The similar caloric expenditure with moderate-intensity aerobic and resistance exercise resulted in a

comparable effect of both training programs on reducing hepatic fat content. In an earlier study by Slentz et al. (4), participants who completed a vigorous aerobic training program with more increased VO_{2max} had a greater liver fat reduction than those with moderate-intensity resistance training. This indicated that the disparity between both exercise types might be due to the different intensity of training. These findings are supported by a recent meta-analysis of continuous high-intensity training effectively reducing liver fat content than moderate-intensity training (20). However, this type of exercise may be unsustainable for many patients with NAFLD. Moderate-intensity exercise is more sustainable, provides most of the hepatic benefits as high-intensity exercise (18,21), and should be recommended for the treatment of NAFLD.

Lifestyle intervention through exercise alone or combined with dietary therapy has been demonstrated to be effective in improving comorbidity associated with insulin resistance in obese patients (22). Our evidence supports the use of exercise training and dietary therapy to reduce liver fat and improve whole-body insulin sensitivity in patients with NAFLD. The improvement in whole-body insulin resistance is likely attributable to minimal weight loss induced by exercise combined with dietary therapy. We further evaluated whether aerobic or resistance training with dietary change could affect insulin sensitivity in any specific organs. The estimates for hepatic and muscle insulin resistance from oral glucose tolerance test data allow us to quantitate insulin sensitivity in nondiabetic subjects. We detected improved insulin secretion after exercise to

<div style="writing-mode: vertical">LIVER</div>

compensate for the underlying insulin resistance and maintain euglycemia in our subjects with NAFLD. We also observed that hepatic benefit is accompanied by improvements in muscle insulin sensitivity after aerobic or resistance training. These data are consistent with the observation that the reversal of muscle insulin resistance through a single bout of exercise decreased hepatic fat content concomitantly with a reduction in hepatic lipogenesis (23). Notably, the benefit of exercise on improvement in muscle but not hepatic insulin sensitivity provides evidence that modulation of skeletal muscle function affects liver metabolism. However, we did not detect the combined effects of exercise and diet on cardiometabolic risk factors. This may be because almost all subjects had plasma levels of glucose, lipoproteins, and inflammatory biomarkers within the laboratory's normal range at baseline.

This study has some limitations. First, we quantified intrahepatic fat using an elastographic technique instead of a magnetic resonance-based technique. Although CAP is less accurate than MRI–proton density fat fraction in detecting all grades of hepatic steatosis (24), it has been shown to correlate with histological grade of hepatic steatosis in a meta-analysis study (7). Also, CAP provides a convenient and patient-friendly method to assess lipid turnover during the lifestyle and dietary interventions for NAFLD. Subsequently, CAP has been used in assessing the change of hepatic steatosis for patients with NAFLD after diet modification and patients with diabetes after glycemic control (25,26). Recently, Wang et al. (27) showed that the change in CAP value was correlated with change in liver fat content assessed by MRI–proton density fat fraction and should be useful as a point-of-care method for monitoring hepatic steatosis. Second, our subjects were medical personnel who may have high motivation to participate in the exercise program. All exercise sessions were completed under supervision, which might improve compliance but also allowed us to effectively assess the effects of exercise. Finally, only 35 participants who actually received the exercise intervention were included in the analysis. Subject attrition can lead to a smaller sample that is underpowered to detect the difference between both exercise groups.

In conclusion, this randomized trial demonstrates that 12 weeks of moderate-intensity aerobic or resistance training and dietary modification is equally effective for reducing liver fat and improving underlying insulin resistance in patients with NAFLD. The greatest benefits were observed with exercise at least 3 times weekly, independent of weight loss. Diet and exercise prescriptions for NAFLD should be tailored to a patient's preference, physical fitness, and comorbidities to facilitate sustained adherence to lifestyle changes.

CONFLICTS OF INTEREST

Study Highlights

WHAT IS KNOWN

✓ Lifestyle intervention involving dietary changes and regular exercise is the cornerstone of management of patients with nonalcoholic fatty liver disease (NAFLD).

✓ The efficacy of aerobic and resistance exercise for the reduction of liver fat in patients with NAFLD is now recognized.

✓ It remains controversial as to which type and frequency of exercise training is more beneficial for patients with NAFLD.

WHAT IS NEW HERE

✓ Aerobic and resistance exercise training for 12 weeks resulted in significant and comparable reductions in hepatic fat content and abdominal adiposity and improvement in insulin resistance in patients with NAFLD.

✓ An increase in the number of weekly exercise sessions was significantly associated with reduction in hepatic fat content.

✓ Weekly exercise training for at least 3 sessions substantially attenuates liver fat accumulation independent of weight loss.

TRANSLATIONAL IMPACT

✓ Moderate-intensity aerobic training and resistance training with dietary modification can provide similar benefits for the management of NAFLD.

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