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Effects of Moderate and Vigorous Exercise on Nonalcoholic Fatty Liver Disease
A Randomized Clinical Trial

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IMPORTANCE Nonalcoholic fatty liver disease (NAFLD) is a prevalent risk factor for chronic liver disease and cardiovascular disease.

OBJECTIVE To compare the effects of moderate and vigorous exercise on intrahepatic triglyceride content and metabolic risk factors among patients with NAFLD.

DESIGN, SETTING, AND PARTICIPANTS In this randomized clinical trial, participants with central obesity and NAFLD were recruited from community-based screening in Xiamen, China, from December 1, 2011, through December 25, 2013. Data analysis was performed from August 28, 2015, through December 15, 2015.

INTERVENTIONS Participants were randomly assigned to vigorous-moderate exercise (jogging 150 minutes per week at 65%-80% of maximum heart rate for 6 months and brisk walking 150 minutes per week at 45%-55% of maximum heart rate for another 6 months), moderate exercise (brisk walking 150 minutes per week for 12 months), or no exercise.

MAIN OUTCOMES AND MEASURES Primary outcome, change in intrahepatic triglyceride content measured by proton magnetic resonance spectroscopy at 6 and 12 months; secondary outcomes, changes in body weight, waist circumference, body fat, and metabolic risk factors.

RESULTS A total of 220 individuals (mean [SD] age, 53.9 [7.1] years; 149 woman [67.7%]) were randomly assigned to control (n = 74), moderate exercise (n = 73), and vigorous-moderate exercise (n = 73) groups. Of them, 211 (95.9%) completed the 6-month follow-up visit; 208 (94.5%) completed the 12-month follow-up visit. Intrahepatic triglyceride content was reduced by 5.0% (95% CI, −7.2% to 2.8%; *P* < .001) in the vigorous-moderate exercise group and 4.2% (95% CI, −6.3% to −2.0%; *P* < .001) in the moderate exercise group compared with the control group at the 6-month assessment. It was reduced by 3.9% (95% CI, −6.0% to −1.7%; *P* < .001) in the vigorous-moderate exercise group and 3.5% (95% CI, −5.6% to −1.3%; *P* = .002) in the moderate exercise group compared with the control group at the 12-month assessment. Changes in intrahepatic triglyceride content were not significantly different between vigorous-moderate and moderate exercise at the 6- or 12-month assessment. Body weight, waist circumference, and blood pressure were significantly reduced in the vigorous-moderate exercise group compared with the moderate exercise and control groups at the 6-month assessment and in the vigorous-moderate and moderate exercise groups compared with the control group at the 12-month assessment. In addition, body fat was significantly reduced in the vigorous-moderate exercise group compared with the moderate exercise and control groups at the 12-month assessment. After adjusting for weight loss, the net changes in intrahepatic triglyceride content were diminished and became nonsignificant between the exercise and control groups (except for the moderate exercise group at the 6-month assessment).

CONCLUSIONS AND RELEVANCE Vigorous and moderate exercise were equally effective in reducing intrahepatic triglyceride content; the effect appeared to be largely mediated by weight loss.

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Nonalcoholic fatty liver disease (NAFLD) has reached epidemic proportions worldwide and is the most common cause of chronic liver disease.[1] The condition affects 20% to 30% of adults in the general population and 70% to 90% of patients with obesity or diabetes in Western countries.[1,2] In China, approximately 20% of adults in the general population have NAFLD.[3] Nonalcoholic fatty liver disease is closely related to insulin resistance and metabolic risk factors (ie, abdominal obesity, hypertension, dyslipidemia, hyperglycemia).[4] Furthermore, NAFLD has been associated with an increased risk of cardiovascular disease independent of metabolic risk factors.[1]

A retrospective clinical study[5] indicated that vigorous but not moderate exercise was associated with a lower risk of steatohepatitis and advanced fibrosis in patients with biopsy-proven NAFLD. Several small clinical trials[6-9] reported inconsistent findings of short-term exercise programs on intrahepatic lipids among patients with NAFLD. In addition, these studies did not provide dose-response information needed to formulate evidence-based clinical guidelines for NAFLD management. Furthermore, the long-term effect of current physical activity guidelines on NAFLD is uncertain.[10-13]

The current study aimed to compare the effects of moderate and vigorous exercise on intrahepatic triglyceride (IHTG) content and metabolic risk factors among patients with NAFLD. In addition, we also compared the effects of transitioning from vigorous to moderate exercise on IHTG and metabolic risk factors.

Key Points

Question Is vigorous exercise more effective in improving nonalcoholic fatty liver disease than moderate exercise?

Findings In this randomized clinical trial of 220 Chinese adults with abdominal obesity and nonalcoholic fatty liver disease, intrahepatic triglyceride content was significantly reduced by 5.0% in the vigorous exercise group and 4.2% in the moderate exercise group compared with a control group during 6 months. The change in intrahepatic triglyceride content was not significantly different between the vigorous and moderate exercise groups.

Meaning Vigorous and moderate exercise was equally effective in reducing intrahepatic triglyceride content among patients with nonalcoholic fatty liver disease.

Methods

Study Design and Oversight

The current study was a randomized, parallel-group, observer-masked clinical trial designed to compare the effects of vigorous and moderate exercise with control on IHTG content, body fat, and metabolic risk factors among patients with NAFLD. The study protocol can be found in Supplement 1. Eligible trial participants were randomly assigned to vigorous-moderate exercise, moderate exercise, or control groups for 12 months with an allocation ratio of 1:1:1. The randomization schedules were generated using SAS PROC PLAN in SAS statistical software (SAS Institute Inc) and concealed until an eligible participant was ready for enrollment. Patient recruitment and intervention were conducted from December 1, 2011, through December 25, 2013, in Xiamen, China. Data analysis was performed from August 28, 2015, through December 15, 2015.

The trial was overseen by a steering committee and an independent data and safety monitoring board affiliated with the Xiamen University Institutional Review Board. The study protocol and informed consent form were approved by institutional review boards of the First Affiliated Hospital of Xiamen University in China and Tulane University. All patients provided written informed consent before enrollment. The trial was not masked, but study staff who collected data on study outcomes were unaware of study group assignments.

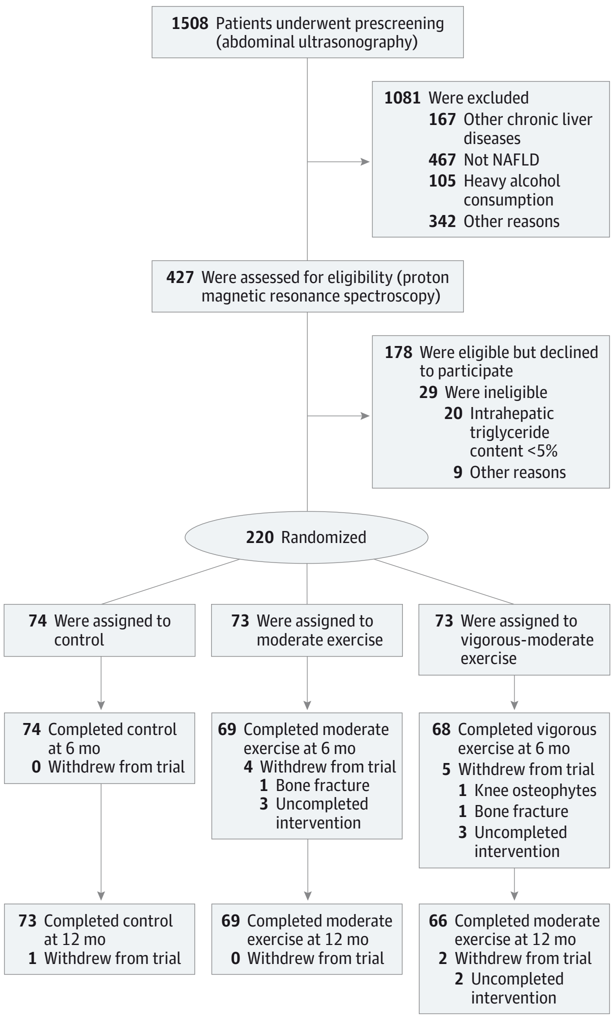
Study Participants

All study participants were recruited from Xiamen City, China, by community-based screening to identify individuals aged 40 to 65 years with central obesity (waist circumference ≥90 cm in men and ≥85 cm in women). Individuals with central obesity were invited to attend a screening abdominal ultrasonographic examination at the study clinic. Those who had ultrasonography-diagnosed NAFLD were invited to confirm their diagnosis by proton magnetic resonance spectroscopy (IHTG content ≥5%). Individuals were excluded if they consumed more than a mean of 140 g of ethanol (10 alcoholic drinks) per week in men and 70 g of ethanol (5 drinks) in women during the past 6 months. Patients were also excluded if they had a history of acute or chronic viral hepatitis, drug-induced liver diseases, or autoimmune hepatitis. In addition, patients were excluded if they had a history of diabetes, uncontrolled hypertension, chronic kidney disease, hyperthyroidism, myocardial infarction within 6 months, or heart failure (New York Heart Association class III or IV). Furthermore, patients were excluded if they were participating in weight loss programs or had a medical condition that limited their exercise capability.

Intervention Programs

Participants assigned to the vigorous-moderate exercise group were instructed to participate in a 6-month vigorous exercise program followed by a 6-month moderate exercise program, whereas participants assigned to the moderate exercise program were instructed to participate in a 12-month moderate exercise program. Participants in the control group were instructed to not change their physical activity routine. All participants attended group health education sessions, which were held biweekly in the first 6 months and monthly in the last 6 months of the intervention. Education sessions were given separately for the intervention and control groups. The health education content (eg, general health knowledge of NAFLD and metabolic diseases, smoking cessation, and elements of a healthy lifestyle) was identical among the randomization groups, with the exception of a behavioral component on adherence to exercise programs that was conducted only in the intervention groups. All study participants were instructed to not change their diet.

Figure 1. Flowchart of Trial Participants



NAFLD indicates nonalcoholic fatty liver disease.

During the vigorous exercise sessions, participants jogged on a treadmill and gradually increased exercise intensity so that their heart rate was 65% to 80% of their maximum predicted heart rate (equivalent to 8.0-10.0 metabolic equivalents). They were instructed to exercise at this intensity for 30 minutes. Their heart rates were monitored by a wireless heart rate monitor (BH Fitness). The maximum predicted heart rate was calculated as 220/min (210/min for women) minus the participant's age.[14] Participants were required to participate in 5 vigorous exercise sessions each week supervised by a study physician at a local community health center. After 6 months of vigorous exercise, participants switched to moderate exercise for another 6 months. In the moderate exercise program, participants were instructed to briskly walk at approximately 120 steps per minute so that their heart rate was 45% to 55% of their maximum predicted heart rate (equivalent to 3.0-6.0 metabolic equivalents) for 30 minutes per session and 5 sessions per week. Participants in the moderate exercise program were required to wear pedometers (Omron Healthcare) and record their daily exercise in a log, which was reviewed weekly by study staff.[15] Participants received follow-up telephone calls from study staff twice per week to assess their adherence to the program and provide suggestions for improvement. Before starting the vigorous and moderate exercise programs, participants were trained for 2 to 4 weeks to achieve the appropriate exercise intensity.

Study Outcomes

The primary outcome was change in IHTG content from baseline to 6 and 12 months after the start of the intervention. The IHTG content was measured using proton magnetic resonance spectroscopy.[16] The secondary outcomes included changes in body weight, waist circumference, body fat, and metabolic risk factors. Body fat mass was quantified using a whole-body dual x-ray system (Hologic Inc). Abdominal visceral fat and subcutaneous fat areas were measured by computed tomography (Siemens Medical Solutions) at the level of the lumbar vertebra.[17] Metabolic risk factors and liver enzymes were measured using standard methods. All study outcomes were measured at baseline and 6- and 12-follow-up visits.

Nutrient intake was estimated by 3 consecutive 24-hour dietary recalls (2 weekdays and 1 weekend day) at baseline and 6 and 12 months. Nutrient intake was calculated based on the nutrient content listed in the Chinese Food Composition Table.[18] Physical activity was assessed using the International Physical Activity Questionnaire (long form) at the baseline examination.[19] Furthermore, trial participants were required to wear a pedometer for 1 week to record their regular physical activity (excluding exercise intervention programs) at baseline, 6 months, and 12 months.

Statistical Analysis

This trial was designed to provide greater than 90% statistical power to detect a 1.76% reduction in IHTG content (SD, 2.35%) at a significance level of .008 (.05/6 for the Bonferroni correction of multiple comparisons) using a 2-tailed test. The proposed group difference and SD of reduction in IHTG content were based on data from previous studies.[6,20] We also assumed an 80% follow-up rate.

Data were analyzed according to participants' randomization assignments, regardless of their subsequent status (intent to treat). A mixed-effects model was used to assess the effects of exercise programs on the change in IHTG content, and an autoregressive correlation matrix was used to correct within-participant correlation for repeated measurements. In this model, participants were assumed to be random effects, and intervention groups, time, and their interaction were assumed to be estimable fixed effects. In addition, we adjusted for weight loss in a secondary analysis to assess its contribution to the change in IHTG content associated with exercise. PROC MIXED of SAS statistical software, version 9.4 (SAS Institute Inc), was used to obtain point estimates and SEs of the treatment effects and to test for differences between treatments. Multiple imputation for missing data in the multivariable analyses was conducted using the Markov chain Monte Carlo method. $P < .008$ (.05/6 comparisons) was considered statistically significant.

Table 1. Baseline Characteristics of Study Participants[a]

Characteristic	Control (n = 74)	Moderate Exercise (n = 73)	Vigorous-Moderate Exercise (n = 73)
Female, No. (%)	46 (62.2)	51 (69.9)	52 (71.2)
Age, y	54.0 (6.8)	54.4 (7.4)	53.2 (7.1)
High school education, No. (%)	15 (20.3)	21(28.8)	23 (31.5)
Current cigarette smoking, No. (%)	18 (24.3)	17 (23.3)	10 (13.7)
Current alcohol drinking, No. (%)	26 (35.1)	21 (28.8)	20 (27.4)
Physical activity, METs/wk	29.1 (9.3)	30.9 (11.1)	31.7 (8.5)
Total energy intake, kcal/d	2140.7 (458.0)	2125.6 (454.4)	2124.8 (454.4)
Fat intake, %	33.3 (6.9)	32.7 (6.3)	31.9 (7.3)
Waist circumference, cm	96.1 (6.9)	95.7 (6.7)	95.2 (7.4)
Weight, kg	72.1 (8.5)	71.1 (10.1)	71.7 (10.1)
BMI	28.0 (2.7)	28.1 (3.3)	27.9 (2.7)
Heart rate, /min	81.7 (12.1)	80.9 (9.7)	80.8 (11.1)
Blood pressure, mm Hg			
Systolic	134.7 (16.7)	131.7 (12.8)	132.1 (15.6)
Diastolic	80.8 (10.6)	81.0 (8.5)	79.7 (9.9)
Plasma glucose, mg/dL	103.5 (9.1)	104.0 (9.3)	102.6 (10.9)
Serum triglycerides, median (IQR), mg/dL	161.1 (126.5-225.7)	161.1 (123.0-202.7)	165.5 (112.4-212.4)
Serum total cholesterol, mg/dL	232.3 (35.0)	239.2 (43.0)	225.6 (44.8)
HDL-C, mg/dL	49.2 (10.8)	50.3 (9.4)	48.3 (9.2)
LDL-C, mg/dL	144.4 (34.5)	146.7 (36.9)	137.9 (44.3)
Visceral fat, cm^2	133.8 (43.2)	135.5 (42.6)	140.9 (41.9)
Subcutaneous fat, cm^2	240.8 (80.8)	225.7 (70.2)	241.4 (72.6)
Body fat, %	33.7 (7.1)	33.6 (5.5)	34.8 (5.3)
Intrahepatic triglyceride content, %	17.5 (11.0)	18.0 (9.9)	18.4 (9.9)

Abbreviations: BMI, body mass index (calculated as the weight in kilograms divided by height in meters squared); HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; METs, metabolic equivalents.

SI conversion factors: To convert glucose to millimoles per liter, multiply by 0.0555; to convert triglycerides to millimoles per liter, multiply by 0.0113; to convert total cholesterol, HDL-C, and LDL-C to millimoles per liter, multiply by 0.0259.

[a] Data are presented as mean (SD) unless otherwise indicated. $P > .05$ for all differences among the 3 groups.

Results

A total of 220 individuals who met all eligibility criteria and were willing to participate in the trial were randomly assigned to the control (n = 74), moderate exercise (n = 73), and vigorous-moderate exercise (n = 73) groups (**Figure 1**). Of them, 211 (95.9%) completed the 6-month follow-up visit, and 208 (94.5%) completed the 12-month follow-up visit. Adherence to the intervention program, defined as participating in 80% or more of the exercise sessions (a mean of 4 of 5 each week) was excellent among those who completed follow-up visits. For example, 67 (98.5%) and 62 (93.9%) individuals participated in 80% or more of the exercise sessions during the 6-month vigorous-exercise and 12-month moderate-exercise interventions in the vigorous-moderate exercise group, and 67 (97.1%) and 66 (95.7%) individuals participated in 80% or more of the exercise sessions during the 6-month and 12-month moderate-exercise intervention, respectively.

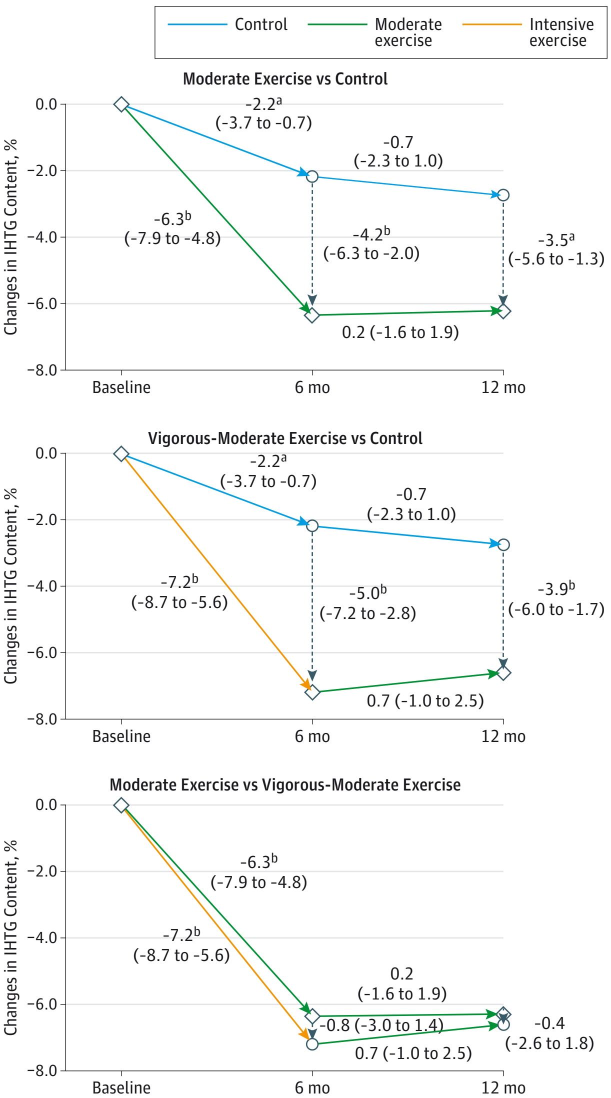
Mean (SD) age was 53.9 (7.1) years, and 149 participants (67.7%) were female. Baseline characteristics were balanced among the 3 groups (**Table 1**). During the 12-month intervention, dietary intake of energy and macronutrients was not significantly different among the 3 groups (eTable 1 in Supplement 2). Regular physical activity (excluding exercise intervention programs) was not significantly different among the 3 groups (eTable 2 in Supplement 2).

Primary Outcomes

Compared with the control group, the IHTG content was reduced by 4.2% (95% CI, −6.3% to −2.0%; $P < .001$) at the 6-month assessment and 3.5% (95% CI, −5.6% to −1.3%; $P = .002$) at the 12-month assessment in the moderate exercise intervention (**Figure 2**). Likewise, the IHTG content was reduced by 5.0% (95% CI, −7.2% to −2.8%; $P < .001$) at 6 months after vigorous exercise and 3.8% (95% CI, −6.0% to −1.7%; $P < .001$) at 12 months after moderate exercise in the vigorous-moderate exercise group compared with the control group (Figure 2). However, the net change in the IHTG content was not significantly different between the vigorous-moderate exercise and moderate exercise groups at the 6-month (−0.8%; 95% CI, −3.0% to 1.4%; $P = .45$) or 12-month (−0.4%; 95% CI, −2.6% to 1.8%; $P = .74$) assessment (Figure 2). Furthermore, transitioning from vigorous exercise to moderate exercise was associated with a nonsignificant increase in the IHTG content (0.7%; 95% CI, −1.0% to 2.5%; $P = .41$) in the vigorous-moderate exercise group.

In a secondary analysis adjusting for weight loss, the IHTG content was reduced by 3.7% (95% CI, −5.7% to −1.7%; $P < .001$) at the 6-month assessment and 2.0% (95% CI, −4.1% to 0.0%; $P = .053$) at the 12-month assessment in the moderate exercise intervention compared with the control group (eTable 3 in Supplement 2). Likewise, the IHTG content was reduced by 2.3% (95% CI, −4.4% to −0.1%; $P = .04$) at 6 months after vigorous exercise and 1.9% (95% CI, −4.0% to 0.3%; $P = .08$) at

Figure 2. Effects of Moderate and Vigorous Exercise on Intrahepatic Triglyceride Content (IHTG)



Numbers in parentheses are 95% CIs.

[a] $P < .005$.

[b] $P < .001$.

12 months after moderate exercise in the vigorous-moderate exercise group compared with the control group after adjusting for weight loss. The adjusted net change in the IHTG content between the vigorous-moderate and moderate exercise groups was −1.4% (95% CI, −0.7% to 3.6%; $P = .20$) at 6 months and −0.2% (95% CI, −1.9% to 2.3%; $P = .86$) at 12 months.

The effect of moderate and vigorous-moderate exercise on IHTG content was not significantly different by subgroups of cigarette smoking, alcohol drinking, high school education, and metabolic syndrome at 6 and 12 months (eTable 4 in Supplement 2).

In a sensitivity analysis using multiple imputed data, net changes in the IHTG content were significantly reduced by −4.1% (95% CI, −6.2% to −2.0%; $P < .001$) and −3.4% (95% CI, −5.5% to −1.2%; $P = .002$) in the moderate exercise group and by −4.8% (95% CI, −6.9% to −2.7%; $P < .001$) and −3.4% (95% CI, −5.6% to −1.3%; $P < .001$) in the vigorous-moderate exercise group at 6-month and 12-month assessments, respectively. No significant differences were found between vigorous-moderate vs moderate exercise groups at 6-month (−0.7%; 95% CI, −2.8% to 1.4%; $P = .51$) or 12-month (−0.1%; 95 CI, −2.2% to 2.0%; $P = .94$) assessments.

Body Weight and Fat

During the 6-month intervention, vigorous exercise significantly reduced weight, waist circumference, body fat mass, and body fat percentage compared with control and moderate exercise (**Table 2**). In addition, vigorous exercise significantly reduced visceral fat compared with moderate exercise and subcutaneous fat compared with control. During the 12-month intervention, both moderate and vigorous-moderate exercise significantly reduced weight and waist circumference. Moreover, vigorous-moderate exercise significantly reduced body fat mass and percentage compared with control and moderate exercise and reduced visceral fat compared with moderate exercise.

Metabolic Risk Factors

During the 6-month intervention, vigorous exercise significantly reduced systolic and diastolic blood pressure compared with control and moderate exercise (**Table 3**). During the 12-month intervention, moderate exercise and vigorous-moderate exercise significantly reduced blood pressure compared with control. Both vigorous and moderate exercise did not significantly reduce fasting glucose or lipid levels during the 6-month or 12-month intervention.

Liver Enzymes

Changes in serum alanine transaminase and γ-glutamyl transferase levels did not significantly differ among the 3 groups during the 6- or 12-month intervention. However, serum aspartate aminotransferase was significantly increased in the vigorous exercise group compared with the moderate exercise group during the 6-month intervention (Table 3).

Adverse Events

No deaths or serious adverse events were reported throughout the study. Two participants (1 in the moderate exercise group and 1 in the vigorous-moderate exercise group) reported bone fractures, which did not occur during exercise sessions.

Discussion

This randomized clinical trial contributes novel findings on the effects of exercise on NAFLD in several aspects. First, this study indicated that vigorous exercise at 65% to 80% of the maximum heart rate and moderate exercise at 45% to 55% of the maximum heart rate for 150 minutes per week are equally effective in reducing the IHTG content among patients with cen-

Table 2. Effects of Moderate and Vigorous Exercise on Body Fat

Outcomes	Changes (95% CIs) Control	Moderate Exercise	Vigorous-Moderate Exercise	P Values Moderate vs Control	Vigorous-Moderate vs Control	Vigorous-Moderate vs Moderate
Weight, kg						
6 mo	−1.49 (−2.10 to −0.88)	−2.02 (−2.65 to −1.40)	−4.33 (−4.96 to −3.70)	.23	<.001	<.001
12 mo	−1.11 (−1.72 to −0.50)	−2.61 (−3.24 to −1.98)	−3.19 (−3.82 to −2.55)	<.001	<.001	.21
Waist circumference, cm						
6 mo	−1.35 (−2.18 to −0.52)	−2.26 (−3.12 to −1.40)	−4.87 (−5.74 to −4.01)	.13	<.001	<.001
12 mo	−0.25 (−1.08 to 0.58)	−2.02 (−2.87 to −1.16)	−2.85 (−3.72 to −1.98)	.004	<.001	.18
Body fat mass, kg						
6 mo	−0.83 (−1.26 to −0.41)	−1.16 (−1.60 to −0.73)	−2.48 (−2.92 to −2.04)	.29	<.001	<.001
12 mo	−0.23 (−0.66 to 0.19)	−0.51 (−0.95 to −0.08)	−1.66 (−2.10 to −1.21)	.37	<.001	<.001
Body fat, %						
6 mo	−0.82 (−1.25 to −0.40)	−0.85 (−1.29 to −0.41)	−2.29 (−2.74 to −1.84)	.93	<.001	<.001
12 mo	−0.29 (−0.73 to 0.14)	0.14 (−0.30 to 0.58)	−1.53 (−1.99 to −1.08)	.17	<.001	<.001
Visceral fat, cm^2						
6 mo	−17.0 (−22.7 to −11.2)	−13.1 (−19.1 to −7.2)	−27.5 (−33.5 to −21.6)	.36	.01	<.001
12 mo	−12.8 (−18.6 to −7.0)	−8.6 (−14.6 to −2.7)	−23.4 (−29.4 to −17.3)	.32	.01	<.001
Subcutaneous fat, cm^2						
6 mo	0.7 (−5.4 to 6.7)	−10.5 (−16.8 to −4.2)	−13.4 (−19.7 to −7.1)	.01	.002	.52
12 mo	−1.6 (−7.6 to 4.5)	−4.2 (−10.4 to 2.1)	−10.2 (−16.5 to −3.8)	.56	.06	.19

tral obesity and NAFLD. Second, most but not all of the effect was mediated by weight loss. Third, only vigorous exercise reduced weight, waist circumference, body fat, and blood pressure at 6 months compared with control. However, moderate exercise reduced weight, waist circumference, and blood pressure but not body fat at 12 months compared with control. Fourth, exercise seems less effective on glucose and lipid reduction in this study population. These findings have important clinical and public health implications.

Several small clinical trials[6-10] assessed the effect of short-term exercise programs on the IHTG content among patients with NAFLD. Johnson and colleagues[6] reported that a 4-week supervised, progressive aerobic exercise program reduced the IHTG content by 21% ($P < .05$) in 12 sedentary obese adults compared with 7 no-exercise controls. Sullivan et al[7] found that moderate exercise for 16 weeks resulted in a 10.3% decrease in the IHTG content in 12 obese persons with NAFLD compared with 6 control patients ($P < .05$). In addition, Keating and colleagues[8] tested the effects of 3 intervention programs with various levels of intensity and dose of aerobic exercise on the IHTG content in an 8-week clinical trial among 48 sedentary overweight or obese adults and documented that all aerobic exercise regimens reduced liver fat with no difference by dose or intensity. In contrast, Shojaee-Moradie et al[9] reported no difference in liver fat during a 6-week exercise program in 10 sedentary overweight men compared with 7 controls. However, these small short-term trials were not able to provide dose-response information to formulate evidence-based clinical guidelines regarding exercise programs in patients with NAFLD.

To our knowledge, this study is the first randomized clinical trial to compare the long-term effect of moderate and vigorous exercise on NAFLD. This trial indicated that moderate and vigorous exercise programs have similar effects on liver fat reduction among obese patients with NAFLD. These results support the current physical activity guidelines (150 minutes of moderate-intensity activity per week) for the management of NAFLD.[11-13] Because moderate exercise is more sustainable and provides most of the benefit of vigorous exercise, it should be recommended for the prevention and treatment of NAFLD.

Weight loss via lifestyle intervention has been documented to play a role in reducing liver fat, and a weight loss of 5% or more seems to be desirable for improving NAFLD.[21] In this trial, exercise programs resulted in a 3% to 6% weight loss, whereas they reduced relative liver fat by 35% to 40% among patients with NAFLD. After adjustment for weight loss, exercise interventions were no longer significantly associated with IHTG content reduction (except for moderate exercise at 6 months) at a predefined significance level of .008. These

Table 3. Effects of Moderate and Vigorous Exercise on Cardiovascular Risk Factors

Outcomes	Changes (95% CIs) Control	Moderate Exercise	Vigorous-Moderate Exercise	*P* Values Moderate vs Control	Vigorous-Moderate vs Control	Vigorous-Moderate vs Moderate
Systolic blood pressure, mm Hg						
6 mo	−3.9 (−5.9 to −2.0)	−5.0 (−7.0 to −3.0)	−10.1 (−12.2 to −8.1)	.46	<.001	<.001
12 mo	−0.001 (−2.0 to 2.0)	−5.5 (−7.6 to −3.5)	−8.3 (−10.4 to −6.2)	<.001	<.001	.06
Diastolic blood pressure, mm Hg						
6 mo	−1.7 (−3.2 to −0.2)	−2.8 (−4.3 to −1.3)	−5.9 (−7.4 to −4.3)	.32	<.001	.006
12 mo	0.4 (−1.1 to 1.9)	−3.5 (−5.0 to −2.0)	−4.1 (−5.7 to −2.6)	<.001	<.001	.56
Plasma glucose, mg/dL						
6 mo	−7.4 (−9.2 to −5.6)	−4.4 (−6.2 to −2.6)	−5.9 (−7.8 to −4.1)	.02	.25	.25
12 mo	−4.7 (−6.5 to −3.0)	−6.1 (−7.9 to −4.3)	−4.9 (−6.7 to −3.0)	.29	.89	.37
Serum triglycerides, mg/dL						
6 mo	−18.0 (−32.5 to −3.5)	−19.8 (−34.9 to −4.8)	−26.3 (−41.5 to −11.1)	.87	.44	.55
12 mo	−27.5 (−42.1 to −12.9)	−14.5 (−29.6 to 0.5)	−20.2 (−35.6 to −4.9)	.22	.50	.60
Serum total cholesterol, mg/dL						
6 mo	−15.3 (−21.0 to −9.5)	−14.0 (−19.9 to −8.0)	−13.0 (−19.0 to −7.0)	.75	.59	.82
12 mo	−11.1 (−16.8 to −5.3)	−14.2 (−20.1 to −8.2)	−9.5 (−15.6 to −3.5)	.46	.72	.29
HDL-C, mg/dL						
6 mo	−0.7 (−2.0 to 0.6)	1.0 (−0.3 to 2.4)	0.5 (−0.9 to 1.9)	.07	.22	.59
12 mo	0.02 (−1.3 to 1.4)	0.4 (−1.0 to 1.7)	1.5 (0.1 to 2.9)	.73	.13	.26
LDL-C, mg/dL						
6 mo	−9.8 (−15.2 to −4.5)	−6.2 (−11.7 to −0.6)	−7.4 (−13.0 to −1.8)	.35	.53	.76
12 mo	−4.5 (−9.8 to 0.9)	−6.7 (−12.3 to −1.2)	−6.3 (−12.0 to −0.7)	.56	.64	.92
Alanine transaminase, U/L						
6 mo	−3.3 (−5.9 to −0.8)	−2.7 (−5.3 to −0.1)	−4.1 (−6.8 to −1.5)	.73	.67	.45
12 mo	−1.3 (−3.8 to 1.3)	−2.2 (−4.8 to 0.4)	−2.7 (−5.3 to −0.01)	.62	.45	.80
Aspartate aminotransferase, U/L						
6 mo	0.2 (−1.1 to 1.5)	−1.3 (−2.7 to 0.1)	1.8 (0.4 to 3.2)	.12	.11	.002
12 mo	0.3 (−1.0 to 1.6)	−0.9 (−2.3 to 0.4)	0.8 (−0.6 to 2.2)	.21	.63	.09
γ-Glutamyltransferase, U/L						
6 mo	−1.3 (−4.8 to 2.2)	−3.8 (−7.4 to −0.2)	−0.4 (−4.0 to 3.2)	.32	.73	.19
12 mo	−1.7 (−5.2 to 1.9)	−0.4 (−4.0 to 3.2)	−2.7 (−6.4 to 1.0)	.61	.69	.37

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

SI conversion factors: To convert glucose to millimoles per liter, multiply by 0.0555; to convert triglycerides to millimoles per liter, multiply by 0.0113; to convert total cholesterol, HDL-C, and LDL-C to millimoles per liter, multiply by 0.0259; to convert aspartate aminotransferase and γ-glutamyltransferase to microkatals per liter, multiply by 0.0167.

findings suggest that the effect of the exercise intervention on the IHTG content reduction was most likely mediated by weight loss.

Although exercise has been recommended as an important weight loss strategy, the exercise intensity required to achieve optimal benefit continues to be the source of considerable uncertainty and debate. Moderate-intensity aerobic exercise has been documented to induce modest reductions in weight and waist circumference in overweight and obese populations.[22] However, there is little conclusive evidence for more favorable effects with high-intensity exercise than with moderate-intensity exercise on weight loss.[23] Jakicic and colleagues[24] compared the effects of different durations and intensities of exercise on 12-month weight loss in a randomized trial of 201 sedentary overweight women. Significant weight loss was achieved among all exercise groups with no differences based on exercise durations and intensities. Ross and colleagues[25] also reported no difference in waist circumference reduction according to exercise amount and intensity in a 24-week randomized trial among 217 abdominally obese adults. Our data indicated that vigorous but not moderate exercise significantly reduced body weight and waist circumference during the 6-month intervention. However, moderate exercise significantly reduced body weight and waist circumference during the 12-month intervention. Our study suggests that short-term vigorous exercise and long-term moderate exercise programs could be recommended for weight reduction in obese individuals.

In this trial, vigorous but not moderate exercise significantly reduced body fat and visceral fat. A meta-analysis[26] of clinical trials suggests that there seems to be a threshold for exercise intensity to have an effect on the reduction of visceral fat. Several clinical trials[27-29] indicated that vigorous or moderate to vigorous exercise reduced visceral fat, whereas another trial[26] found that low to moderate exercise did not reduce visceral fat. Irving and colleagues[30] compared the effect of low-intensity and high-intensity aerobic exercise with a no-exercise control on abdominal adiposity among 27 obese women and reported that only high-intensity exercise reduced abdominal fat and visceral fat during a 16-week intervention. Our study is the first large trial, to our knowledge, to compare the effect of moderate and vigorous exercise on visceral fat reduction. Our study suggests that vigorous exercise may be required for reducing visceral fat among obese individuals.

Our study finding that aerobic exercise reduced blood pressure was consistent with previous clinical trials.[31] However, exercise did not significantly reduce lipid or glucose levels in our study. Previous clinical trials[32,33] also reported inconsistent effects of aerobic exercise on low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and glucose levels in participants without dietary intervention.

This study has some limitations. First, to test the effect of transitioning from vigorous to moderate exercise on NAFLD, the vigorous exercise intervention lasted for only 6 months. Future trials should compare the long-term effects of vigorous and moderate exercise on the IHTG content and metabolic risk factors among patients with NAFLD. Second, the primary outcome was the IHTG content instead of biopsy-proven fibrosis or steatosis. However, the IHTG content measured by magnetic resonance spectroscopy is highly reproducible and correlated with the histologic features of fibrosis and steatosis.[34,35] Magnetic resonance spectroscopy is regarded as the most accurate noninvasive method of measuring liver fat among patients with NAFLD in clinical practice.[36] In addition, the IHTG content is more sensitive than the steatosis grade determined by histologic analysis in quantifying changes in liver fat content and has been recommended for this specific use in clinical trials.[37] In our study, magnetic resonance spectroscopy was performed using a standard protocol based on 1.3-ppm lipid methylene protons to avoid measurement variations.[38] Third, dietary calorie and fat intake were not controlled in this study because we aimed to examine isolated effects of exercise on NAFLD. Future clinical trials should examine the effects of combined intervention strategies on long-term outcomes of NAFLD.

Conclusions

This study indicates that vigorous and moderate exercise were equally effective in reducing IHTG content, whereas vigorous exercise might have additional benefits in reducing weight, body fat, and blood pressure among patients with NAFLD. For individuals who might have difficulty engaging in vigorous exercise, moderate exercise would have the same effects on the prevention and treatment of NAFLD. Most of the effect of the interventions on the IHTG content appeared to be mediated by weight loss.

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