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Exercise and NAFLD: Is It Worth the Effort?

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Nonalcoholic fatty liver disease (NAFLD) represents a spectrum of liver abnormalities, characterized by an increase in intrahepatic triglyceride (IHTG) content that can progress to inflammation and fibrosis. In addition, NAFLD is associated with an increased risk of serious cardiometabolic abnormalities, including atherogenic dyslipidemia, hypertension, metabolic syndrome, diabetes, and coronary heart disease.⁽¹⁾ Lifestyle therapy that is targeted toward decreasing energy intake and increasing physical activity is considered the cornerstone of therapy for patients with NAFLD. The liver is very responsive to calorie restriction and weight loss. Even 48 hours of consuming a low-calorie diet decreases IHTG content,⁽²⁾ and progressive 5%, 11%, and 16% diet-induced weight loss decreases IHTG content by 15%, 50%, and 65%, respectively, in people with NAFLD and moderate steatosis (~10% liver volume as triglyceride).⁽³⁾ Moreover, 5%-10% weight loss improves most histological features of NAFLD, including NAFLD activity score, steatosis, inflammation, and ballooning, and 10% weight loss decreases hepatic fibrosis.⁽⁴⁾ However, the type, intensity, and volume of exercise needed for optimal therapeutic effects in patients with NAFLD are not clear.

Recently, the results of a 12-month, randomized, controlled trial, conducted by Zhang et al. in Xiamen, China, that evaluated the effects of moderate and vigorous endurance exercise training on IHTG content and cardiometabolic risk factors in people with NAFLD was reported in *JAMA Internal Medicine*.⁽⁵⁾ This trial represents the largest and longest duration exercise study in people with NAFLD (Table 1). A total of 220 men and women with NAFLD participated in this study (54% women; mean age, ~54 years; mean body weight, ~72 kg; mean BMI, ~28 kg/m²; and mean IHTG content, ~18%). Participants were randomized in a 1:1:1 allocation to one of the following three groups: (1) no-exercise control group (NE); (2) vigorous-moderate exercise group (V-ME), in which subjects performed supervised vigorous intensity exercise (jogging at 65%-80% of maximal heart rate) for 30 minutes, 5 days/week for 6 months followed by moderate-intensity exercise (brisk walking at 45%-55% of maximal heart rate) for 30 minutes, 5 days/week for 6 months; or (3) moderate intensity exercise group (ME), in which subjects performed supervised moderate intensity exercise for 30 minutes, 5 days/week for 12 months.

At 6 months, IHTG content decreased more in the V-ME (by 5.0%) and ME (by 4.2%) groups than in the NE control group, without a difference between the two exercise groups. At 12 months, the decline in IHTG content was also greater in the both the V-ME (by 3.8%) and ME (by 3.5%) groups than the NE control group, without a difference between the two

exercise groups. Body weight in the V-ME, ME, and NE groups decreased by 4.3, 2.0, and 1.5 kg, respectively, at 6 months and by 3.2, 2.6, and 1.1 kg, respectively, at 12 months. The significance of the beneficial effect of exercise training on IHTG content at 6 and 12 months remained after adjusting for changes in body weight. Serum alanine transaminase concentrations did not change in any group after 6 or 12 months of intervention.

This study makes an important contribution to our understanding of the therapeutic effect of regular exercise in people with NAFLD. The data demonstrate that long-term (1-year) regular endurance exercise causes a sustained decrease in IHTG content. Moreover, by adjusting for changes in body weight among treatment groups, their results suggest that the effect of exercise on IHTG was mediated by both a decrease in body weight and a weight loss-independent effect of exercise itself. However, the calculated effect of exercise alone on IHTG content was small, accounting for around a 2% decline in IHTG content at 12 months, and neither exercise intervention had an effect on serum alanine transaminase concentration. These results are consistent with data from previous randomized, controlled trials, which have shown that exercise training without weight loss has small, albeit statistically significant, effects on IHTG content (Table 1) and does not affect serum alanine transaminase concentrations.⁽⁶⁾

There are several issues that need to be considered in translating the results from the study by Zhang et al. into clinical practice. First, the moderate and vigorous exercise training intervention in this study are identical to the lowest and highest range of exercise intensity and volume recommended by the Department of Health and Human Services, the American College of Sports Medicine, and the American Heart Association to achieve health benefits in adults. Therefore, the exercise interventions tested in this study are already recommended for all adults, with or without NAFLD. Second, physical activity has considerable health benefits for people at high risk for cardiometabolic diseases, because endurance and resistance exercise increase insulin sensitivity and decrease the risk of developing diabetes or dying from coronary heart disease.⁽⁷⁾ Third, the study by Zhang et al. was conducted in an Asian population, which is known to be at increased risk of developing NAFLD at much lower body mass index (BMI) values than white, Hispanic, and black populations.⁽⁸⁾ Therefore, it is not known whether the results from this study apply to other ethnic/racial groups. Nonetheless, the consistency of their results with those of previous studies, as summarized in Table 1, suggest that their findings are likely relevant to other populations. Fourth, compliance with the exercise intervention in the study by Zhang et al. was extraordinary because of comprehensive supervision and monitoring, which is not practical in a typical clinical setting; more than 90% of participants in the ME and V-ME groups participated in 80% or more of the exercise sessions. Finally, the importance of the exercise interventions studied by Zhang et al. in the management of NAFLD cannot be fully appreciated without an evaluation of the histological features of NAFLD that determine disease severity.

What can be learned from this study that affects the clinical management recommendations for patients with NAFLD? Despite the considerations noted in the previous paragraph, the results from the study by Zhang et al., in conjunction with the data from previous randomized, controlled trials, help put the role of endurance exercise in proper perspective

with some good and bad news. Moderate endurance exercise (brisk walking, 30 minutes/day, 5 days/week) is probably just as good as vigorous endurance exercise (jogging, 30 minutes/day, 5 days/week) in reducing IHTG content. However, even though most people are more likely to adhere to a moderate-intensity than a vigorous-intensity exercise program,⁽⁹⁾ adherence with any exercise intervention is often poor and the compliance achieved by Zhang et al. is unlikely to occur in real life. Clearly, endurance exercise does decrease IHTG content, but the effect is likely to be small unless there is concomitant weight loss. Therefore, weight loss is the key lifestyle intervention component that is needed to effectively reduce IHTG content and improve liver histology in patients with NAFLD.

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TABLE 1.
Characteristics and Results of Randomized, Controlled Trials Evaluating the Effect of Exercise Training on IHTG Content

Study (Author/Year)	N	Age (Years) *	BMI (kg/m ²) *	Exercise			Weight Loss	IHTG Content (%)	
				Type	Duration (wks)	Intensity		Before	After
Zhang et al. 2016 ⁽⁵⁾	220	54	28	ET	26	A) No exercise control	Yes	17.5	15.3
						B) High	Yes	18.4	11.2
						C) Moderate	Yes	18.0	11.7
	220	54	28	ET	52	A) No exercise control	Yes	17.5	14.6
						B) High then Moderate	Yes	18.4	11.9
						C) Moderate	Yes	18.0	11.9
Cuthbertson et al. 2016 ⁽¹⁰⁾	50	51	30	ET	16	A) No exercise control	No	16.0	14.6
						B) Low to Moderate	Yes	19.4	10.1
Keating et al. 2015 ⁽¹¹⁾	47	44	33	ET	8	A) No exercise control	No	7.7	8.8
						B) High	Yes	8.4	6.0
						B) 90-135	Yes	8.4	6.0
						C) 180-240	Yes	9.4	6.8
						D) 90-135	No	4.5	3.7
Sullivan et al. 2012 ⁽¹²⁾	18	48	38	ET	16	A) No exercise control	No	21.4	23.9
						B) Moderate	No	20.4	17.5
Hallsworth et al. 2011 ⁽¹³⁾	19	56	32	RT	8	A) No exercise control	No	11.2	11.5
						B) 50%-70% IRM	No	14.0	12.2
Johnson et al. 2009 ⁽¹⁴⁾	23	48	32	ET	4	A) No exercise control	No	9.2	9.4
						B) High	No	8.6	6.8
Shojaee-Moradie et al. 2007 ⁽¹⁵⁾	17	50	28	ET	6	A) No exercise control	No	3.9	5.2
						B) High	No	4.0	4.3

High = high-intensity endurance exercise training (60%-85% of maximal heart rate, VO_{2peak}, or VO_{2max}); Moderate = moderate-intensity endurance exercise training (45%-55% of VO_{2peak}); Low = low-intensity endurance exercise training (30% of heart rate reserve); IRM = one repetition maximum.

* Values estimated from group data.

Abbreviations: ET, endurance exercise training; RT, resistance training.