

Invited Commentary

LESS IS MORE

Moderate Exercise for Nonalcoholic Fatty Liver Disease

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Long-term nutritional excess coupled with reduced physical activity has fueled the rise of obesity-related metabolic conditions. In many countries with high population density, overnutrition is now responsible for more morbidity than under-



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nutrition. Nonalcoholic fatty liver disease (NAFLD) is 1 of the consequences of the imbalance between caloric intake and expenditure and is a leading cause of chronic liver disease, affecting up to 30% of the world's population. Nonalcoholic fatty liver disease is associated with significant morbidity, particularly for those with the progressive version nonalcoholic steatohepatitis. Nonalcoholic steatohepatitis may progress to cirrhosis, with mortality primarily driven by cardiovascular disease and malignant tumors. Nonalcoholic fatty liver disease is strongly associated with visceral obesity and may contribute independently to the development of other metabolic conditions, such as diabetes, cardiovascular disease, and hyperlipidemia.

Given that NAFLD stems from overnutrition, it is not surprising that weight loss is the first-line treatment for all stages of the condition. Data on the beneficial effects of weight loss are consistent, and the extent of histologic improvement correlates with the percentage of body weight lost. For example, as little as 5% can reduce intrahepatic triglyceride content, but higher degrees of weight loss (>7%-10%) are needed to reverse histologic features associated with disease progression (nonalcoholic steatohepatitis and fibrosis).¹ In contrast, there is a paucity of high-quality evidence to support exercise specifically as a primary treatment for NAFLD.² One study³ suggests that aerobic and resistance exercise can decrease hepatic steatosis, improve cardiovascular health, and decrease insulin resistance even if weight loss is not achieved. However, current guidelines provide little direction on the type or level of exercise intensity needed to benefit patients with NAFLD.

In this issue of *JAMA Internal Medicine*, Zhang et al⁴ present the results of a clinical trial examining the effects of exercise on intrahepatic triglyceride content in 220 individuals with NAFLD randomized to 3 different exercise programs (vigorous-moderate, moderate, and control groups). Patients in the vigorous-moderate group exercised 30 minutes 5 days per week for 6 months at high intensity (goal, 65%-80% of the maximum predicted heart rate [8-10 metabolic equivalents]) followed by 6 months of a moderate-intensity regimen (goal, 45%-55% of the maximum predicted heart rate [3-6 metabolic equivalents]).

The moderate exercise group maintained this moderate-intensity regimen for 12 months, and the control group did not change their level of physical activity from baseline. Study participants were asked to continue their typical diet. Both vig-

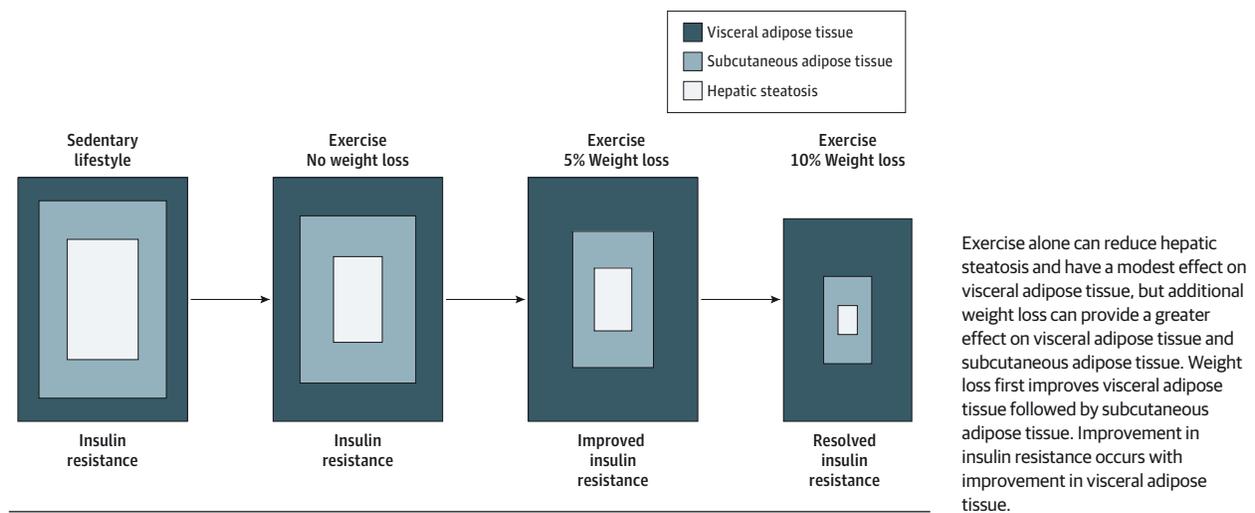
orous-moderate and moderate exercise reduced intrahepatic triglyceride content at 6 and 12 months when compared with the control arm (-5.01% and -3.85% and -4.16% and -3.48%, respectively, $P < .001$). When the vigorous-moderate and moderate groups were directly compared, reductions of intrahepatic triglyceride content at 12 months were similar, suggesting that high-intensity exercise did not offer additional benefit with respect to improving hepatic steatosis.

Another study⁵ found that more intense exercise is needed to more significantly reduce hepatic steatosis, inflammatory markers, and metabolic parameters. The study by Zhang and colleagues⁴ is the first prospective randomized trial, to our knowledge, to find that a lower-intensity exercise program may be beneficial to patients with NAFLD during 12 months. It is possible that a 12-month vigorous exercise group would have had even further benefit compared with the other groups. If 6-month data are examined, patients completing the intense exercise phase of the vigorous-moderate exercise group had significantly more weight loss and reductions in body fat mass, blood pressure, and visceral adipose tissue compared with the moderate exercise and control groups. Interestingly, improvements in visceral adipose tissue persisted in the vigorous-moderate exercise group at 12 months after intensity had been reduced and despite mild weight gain during the latter 6 months.

Visceral adipose tissue plays a central role in the pathogenesis of NAFLD and insulin resistance, and an exercise routine with the greatest effect on visceral adipose tissue should be the goal. The results in the moderate exercise group are similar to studies evaluating the role of lower-intensity resistance training. Many of these studies suggest that resistance training reduces intrahepatic fat, but its effects on visceral adipose tissue and other metabolic parameters have not been convincing. Loss of visceral adipose tissue typically occurs when patients lose 5% to 10% of their initial body weight.⁶ High-intensity exercise burns more calories and can facilitate faster weight and visceral adipose tissue loss.⁷ The benefits of exercise and weight loss on adiposity and insulin resistance are shown in the **Figure**. Although not yet studied rigorously in patients with NAFLD, an exercise plan that incorporates strength and aerobic training or one that incorporates short bursts of high-intensity exercise may be the most beneficial.

Even if high-intensity exercise is ideal, participation in it is limited. A previous study⁸ found that patients with NAFLD engage in less physical activity than healthy controls. The study by Zhang et al⁴ provides encouragement that maintaining a moderate-intensity exercise program is feasible (96% completed the 12-month program). Because the trial did not include a diet arm, it is impossible to compare the benefits of exercise that are independent of weight loss from those attributable to weight loss alone. However, when the authors

Figure. Benefits of Exercise and Weight Loss on Adipose Tissue Compartments and Insulin Resistance



adjusted for weight loss, they found that much but not all of the effect on intrahepatic triglyceride content was explained, suggesting that exercise and weight loss are likely to benefit NAFLD.

There are important genetic and environmental determinants of NAFLD, and the disease phenotype can differ greatly among ethnic groups. Compared with whites and Hispanics, Asians develop NAFLD at a lower body mass index and have lower rates of obesity. Although Asians tend to have lower body mass indexes, they have relatively higher levels of visceral adipose tissue and are more susceptible to metabolic disease. Thus, the findings by Zhang et al,⁴ although important, may not be generalizable to other populations or ethnicities. Another factor that limits generalizability is that patients with dia-

betes were excluded, and NAFLD is present in 40% to 70% of patients with diabetes.

Lifestyle intervention is the cornerstone of treatment for NAFLD because it treats the root cause of the disease and its comorbidities. For clinicians, the study by Zhang et al⁴ validates that encouraging patients to engage in moderate-intensity activity not only is better than nothing at all but also has reasonable efficacy compared with more intense regimens if it is sustained. This study also suggests that if patients are motivated, it is likely that higher-intensity exercise may have an incremental positive effect on drivers of disease progression, such as visceral adipose tissue, and provide superior cardiovascular benefit, which is more likely to favorably affect long-term outcomes in patients with NAFLD.

ARTICLE INFORMATION

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