Exercise: A Fundamental Component of Lifestyle Management in Obesity-Related Liver Disease

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Abstract

Background and Objective

Recently a novel notion has arisen among the scientific community: non-alcoholic fatty liver disease; NAFLD, which represents a spectrum of conditions ranging from asymptomatic simple steatosis to steatohepatitis and cirrhosis is strongly associated with obesity and its sustaining conditions and increased risk of CVD, and are correlated with all-cause mortality. These facts indicate that therapeutic strategies substantially recuperating NAFLD are necessary. At present, weight loss is the only strategy confirmed to reduce hepatic steatosis. For this reason, dietary restriction focusing on weight loss is the established cornerstone for the management of this disease. In contrast, increased physical activity alone is not recommended as a useful strategy against NAFLD because it results in only moderate weight loss. However, outside the field of NAFLD, the benefit of exercise e.g., improved insulin resistance, lipids profile, inflammation, and oxidative stress and also, functional capacity, quality-of-life, well-being, and all-cause mortality beyond assisting weight loss, are apparent. Although weight loss should be the optimal goal, a beneficial independent effect of exercise per se and additive benefit of exercise when coupled with diet restriction should be investigated as a second practical strategy in NAFLD. In addition, there is an obvious need to understand the effectors of exercise-mediated benefits in NAFLD, including physical activity dose, modality, and the relative importance of structured exercise. Clarification of these effectors will enable the formulation of effective and time-efficient physical activity programs that may ultimately enhance patient benefit, participation and adherence. With this in mind, we established the following research objectives and conducted the relevant studies;

Objective 1: to determine whether exercise without dietary restriction in obese, middle-aged men who had abnormal liver function and suspicious liver fibrosis - can influence the pathophysiology of abnormal liver function.

Objective 2: to determine whether the addition of an exercise regimen to dietary restriction can provide additive benefits on hepatic steatosis and its underlying pathophysiology.

Objective 3: to estimate the benefit of varying dose of physical activity in lifestyle management on pathophysiology of NAFLD from hepatic steatosis to fibrosis.

Method

The 12-week dietary and exercise program were performed from 2006 to 2013 at the University of Tsukuba, Japan. Obese, middle aged men (BMI > 25 kg/m^2, according to domestic obesity guidelines) were recruited from Ibaraki prefecture.

Objective 1: A total of 108 subjects who completed a exercise program without any dietary restriction were analyzed in this study; these results were compared to those of 104 subjects who completed a dietary restriction program. Furthermore, 42 of these subjects (from both groups) who had abnormal liver function and suspicious liver fibrosis by NAFLD fibrosis score were analyzed to obtain a more concrete outcome for exercise effects.

Objective 2: A total of 72 men trained for 12 weeks and were placed into two different intervention groups (diet plus exercise (n=52) or diet alone (n=20)).

Objective 3: A total of 169 subjects performed diet restriction, 40 of whom carried out lesser than 150 $min \cdot wk^{-1}$ of moderate to vigorous intensity physical activity (MVPA), 42 in 150-250 $min \cdot wk^{-1}$ and 87 in more than 250 $min \cdot wk^{-1}$, were entered into the current study and analyzed.

Result

Objective 1: In exercise training, although the magnitude of body-weight loss (-3.1% vs. -8.5%), waist circumference (-4.0% vs. -7.1%) and visceral adipose tissue area (-12.2% vs. -22.5%) was significantly more modest than that achieved by dietary restriction, exercise elicited equivalent reductions in serum ALT and γGT levels (-20.6% vs. -16.1% and -25.7% vs. -34.0%) and equivalent improvement of insulin resistance (-29.7% vs. -26.9%). Moreover, exercise remarkably increased the serum adiponectin level (+33.4% vs. +15.1%). Importantly, for subjects with abnormal liver function and suspicious liver fibrosis, exercise was effective in reducing the serum levels of inflammatory and oxidative stress markers - ferritin and TABRS (-25.0% vs. +1.1% and -33.5% vs. -10.5%). Exercise benefits the management of NAFLD independent of detectable weight loss. Particularly, these effects seem to be acquired through an improvement in the hepatic inflammatory condition and its related oxidative stress levels.

Objective 2: Subjects in the diet + exercise group, compared with those in the diet alone group, elicited additive effects on the degree of hepatic steatosis (-82.6% vs. -60.0%) and body weight (-13.3% vs. -8.9%) accompanied by an improvement in serum marker levels: ferritin (-16.1% vs. -2.1%), lipid peroxidation (-31.8% vs. +4.8%) and adiponectin and leptin (+27.4% vs. +2.6% and -74.4% vs. -30.2%). Consequently, subjects in the diet + exercise group achieved further improvement in insulin resistance (HOMA-IR, -63.6% vs. -40.0%). We concluded that the addition of exercise to a diet regimen potentiates the benefits in NAFLD management through further improvement of hepatic steatosis, inflammatory and oxidative stress levels, adipokine imbalance, and thereby insulin resistance.

Objective 3: In comparison with subjects with MVPA volume of < 150 min·wk^{-1}, those with 250 min·wk^{-1} led to a considerable improvement independent of detectable weight loss in the severity of visceral adipose fat area (-18.2% vs. -38.6%), levels of ferritin (+3.4% vs. -11.8%), lipid peroxidation (-0.5% vs. -15.6%), adiponectin (+3.3% vs. +17.9%), and lipid profiles levels of HDLC and TG (+3.0% vs. 9.6% and -7.1% vs. -12.2%). For patients with severity of NAFLD, MVPA volume of $\geq$ 250 min·wk^{-1} combined with diet restriction is recommended. Such exercise habituation would provide the health benefits related to hepatic steatosis and its progression through oxidative stress and related inflammation, and enhanced lipolysis.

Conclusion

The results of this study have shown that exercise per se (**Objective 1**) or exercise when coupled with diet restriction (**Objective 2**) beneficially modulates liver fat content through a modification of inflammation and its related oxidative stress levels in the liver. The benefits are unrelated to weight loss and closely associated with the greater amounts of moderate to vigorous intensity physical activity i.e. $\geq$250 min·wk^{-1} (**Objective 3**). Even though weight loss would be an optimal goal for the obesity-related liver disease, there are practical challenges to achieving sustainable weight loss with lifestyle management. Thus, an independent benefit of regular exercise would provide a second practical intervention target. These important benefits of exercise should be emphasized and ideally delivered by using a multidisciplinary approach.