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Are Exercise Benefits in Non-Alcoholic Fatty Liver Disease Due to Increased Autophagy?

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Non-alcoholic fatty liver disease (NAFLD) is the most frequent form of liver disease in the United States and most countries for which data is available. The spectrum of NAFLD includes simple hepatic steatosis with accumulation of triglycerides in the hepatocytes, non-alcoholic steatohepatitis (NASH) characterized by hepatocyte ballooning, lobular inflammation and fibrosis in addition to triglyceride accumulation that progresses to cirrhosis. Because NASH can progress to cirrhosis, clinicians have generally focused on therapies that target hepatic lipid accumulation (obeticholic acid, a synthetic bile salt, that increases hepatic fatty acid oxidation), vitamin E (antioxidant that protects hepatic oxidant stress) and pioglitazone (insulin sensitizer). However, lack of universal or consistently predictable benefit and potential for adverse effects have limited approval by regulatory agencies or widespread clinical use.

A number of epidemiological studies have reported that sarcopenic obesity is a common accompaniment of NAFLD. Although the mechanisms responsible for sarcopenia (loss of muscle mass) in sarcopenic obesity have not been identified, body composition studies in NAFLD have suggested that a lower muscle-to-fat ratio is associated with more severe histological injury. Interestingly, metabolic disturbances contribute to cardiovascular and cerebrovascular events, the major causes of death in NAFLD. These data provide the rationale for targeting the skeletal muscle in NAFLD(1) to elicit lifestyle modifications that improve cardiovascular and cerebrovascular morbidity and mortality. The literature on exercise in NAFLD shows significant benefits on hepatic steatosis, serum transaminases, lipid profile and glycemic control that can potentially lower cardiovascular and cerebrovascular events, even though these have not been directly evaluated. Interestingly, both endurance and strength exercise are beneficial in NAFLD(3). Two interesting questions are how does exercise benefit NAFLD and what is/are the mediators of the muscle-liver axis whereby the muscle regulates hepatic metabolism.

In the accompanying review by Chun et al. (4), the mechanisms by which exercise benefits NAFLD has focused primarily on autophagy. Extensive preclinical and consistent but very limited data in patients with NAFL suggest impaired hepatic autophagy in NAFLD. Hepatic autophagy may improve NAFLD by reversing oxidative stress and mitochondrial dysfunction that contribute to hepatocyte injury and stellate cell activation and fibrosis. Consistently, preclinical data support the interpretation that inducing autophagy decreases hepatic lipid accumulation and fibrosis in NAFLD. Exercise is an effective non-

pharmacological intervention that promotes improvement of liver function tests in NAFLD and in the accompanying article, the thesis is that exercise is beneficial through enhanced autophagy in the skeletal muscle and possibly liver. The mechanisms by which exercise stimulates hepatic autophagy are currently areas of active investigation as mentioned in the article by Chun et al (4). There is emerging evidence that exercise induced secretion of irisin and potentially other myokines promote browning of fat and may have direct effects on hepatocyte triglyceride accumulation (4). However, the beneficial effects of exercise cannot be ascribed only to stimulation of autophagy. Exercise also improves oxidative stress and insulin sensitivity, both of which are beneficial in NAFLD. Exercise also improves microcirculatory and endothelial dysfunction, major contributors to morbidity and mortality in NAFLD. In fact, interventions that target non-hepatic accompaniments of NAFLD are critical and exercise with calorie restriction does provide such a global benefit. Molecular responses to exercise include activation of mTORC1, increased phosphorylation of AMPK, a reduction in myostatin expression, and myokine mediated metabolic effects amongst a host of other alterations. Longitudinal data are needed to determine the mechanisms by which exercise produces metabolic organ triad homeostasis in patients with NAFLD. These data will provide the rationale to optimize exercise and lifestyle modifications, including dietary alterations to reverse hepatic and non-hepatic organ dysfunction, and clinical consequences in NAFLD and metabolic syndrome.

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