Interdisciplinary Approach to Examine the Effects of Lifestyle Modifications on Nonalcoholic Fatty Liver Disease

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A critical complication of the obesity epidemic experienced in Westernized societies is nonalcoholic fatty liver disease (NAFLD). NAFLD, fatty liver not due to alcohol consumption, is the most common chronic liver disease and associated with increasing morbidity, mortality, and demand for liver transplantation. NAFLD is a progressive disease with a histological spectrum ranging from hepatic steatosis to nonalcoholic steatohepatitis, advanced fibrosis, and cirrhosis. Approximately one third of all US adults (90 million) have fatty livers, with prevalence rates as high as 75-100% in the obese and morbidly obese. With growing health problems associated with NAFLD, major questions facing research scientists and health care providers are what are the mechanisms responsible for NAFLD development and what is the best treatment strategy. Since drug interventions appear to be only marginally successful, the cornerstone therapy for NAFLD remains lifestyle modifications of exercise and weight loss. However, while recent cross-sectional observations suggest that being more physically active is inversely associated with NAFLD, studies which attempt to identify molecular mechanisms underlying the effects of lifestyle modifications on NAFLD are lacking. To address these clinical questions, we have taken an interdisciplinary approach with collaborations from experts in multiple departments and facilities at the University of Missouri, including Nutrition and Exercise Physiology, Hepatology, Veterinary Biomedical Sciences, and VA investigators. In addition, we have utilized a unique animal model, the hyperphagic Otsuka Long-Evans Tokushima Fatty (OLETF) rat that develops obesity, insulin resistance and overt type 2 diabetes, a model which we liken to overeating, sedentary, obese humans. Through a series of experiments, we found that the natural progression pattern of fatty liver disease in the sedentary

OLETF rat closely resembles the human condition (progression from simple hepatic steatosis to hepatocyte ballooning, fibrosis, and inflammation). We also have compelling evidence that hepatic mitochondrial dysfunction is present at an early age and mitochondrial content, function, and mitochondrial health are disrupted with disease progression, suggesting a potential primary event in NAFLD in this animal model. However and perhaps even more important, when OLETF rats are given access to voluntary running wheels and allowed to exercise daily, the initiation and progression of NAFLD is completely prevented. These benefits occur through modification in both peripheral and hepatic factors, including maintenance of glycemic control and enhancement of hepatic mitochondrial content and function. We are currently in the process of translating these very exciting findings in a randomized, human clinical trial examining the impact of different lifestyle modifications in the treatment of NAFLD. Findings from our research group have important public health application, particularly for the 60-80% of Americans who overeat, who are overweight, and who are physically inactive.