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

R Scott Rector, GM Uptergrove, FW Booth, JP Thyfault, and JA Ibdah
Departments of Internal Medicine-Division of Gastroenterology and Hepatology, Biomedical Sciences, Medical Pharmacology and Physiology, Nutrition and Exercise Physiology, University of Missouri. Research Services, HSTM VA Hospital, Columbia, MO.

ABSTRACT
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 US adults (30 million) have fatty livers, with prevalence rates as high as 75-90% 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 conventional 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, Biomedical Sciences, and VA Investigators. In addition, we have utilized a unique animal model, the ob/ob Zucker Long-Evans Tokushima Otsuka (OLETF) rat that develops obesity, hepatic steatosis, insulin resistance and overt type II diabetes, a model which we believe to be evolving, sedentary, obese humans. Through a series of experiments, we have found that the natural progression pattern of fatty liver disease in the sedentary OLETF rat closely resembles the human condition of simple hepatic steatosis to hepatic steatohepatitis, advanced fibrosis and cirrhosis. We also have compiled 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 target in NAFLD in this animal model. However, we have also found that OLETF rats are given access to voluntary running wheels and allow for exercise daily, the initiation and progression of NAFLD is completely prevented. These studies occur through modulation of both peripheral and hepatic factors including maintenance of glycemic control and enhancement of hepatic mitochondrial content and function. We also conclude the cases of translating these very exciting findings in a rodent model into human clinical trials examining the impact of different lifestyle modifications on the treatment of NAFLD. Findings from our research group have important public health application, particularly for the 60-80% of Americans who are overweight, who are physically inactive.

Majority of Americans Do Not Follow a Healthy Lifestyle

According to the 2005 Behavioral Risk Factor Surveillance System, N = 153,605

Interdisciplinary Approach to Combat Lifestyle-Related Diseases
We have established collaborations from experts in multiple departments and facilities at the University of Missouri, including Nutrition and Exercise Physiology, Hepatology, and Biomedical Sciences, as well as VA Medical Center investigators.

Nutrition & Exercise Physiology
Hepatology
Biomedical Sciences
Nonalcoholic Fatty Liver Disease

Being More Physically Active is Associated with Reduced NAFLD in Humans

Heath et al Circulation 1998

Nonalcoholic Fatty Liver Disease (NAFLD) is Reaching Epidemic Levels


Spectrum of Nonalcoholic Fatty Liver Disease

Steatohepatitis

Cirrhosis

20%

20%

Majority of Americans Do Not Follow a Healthy Lifestyle

Sedentary 10 20 30 40 50 60 70 80 90 100

Smokers BMI >25, k/gm2

Consumers fruit/vegetables

Intrauterine

Exercise

<30 minutes

<15 minutes

<7 minutes

<3 minutes

<1 minute

<1 seconds

Reeves MJ and Rafferty AP. Arch Intern Med 2005; 165:854-7

Identification of an Appropriate Model to Study Human Obesity and NAFLD

OTSUKA LONG-EVANS TOKUSHIMA FATTY (OLETF) RAT

Oleksyuk a

Exercise Tokushima

Bellenti ani

Follow a Healthy Lifestyle

L ET O at respective age (p<0.01). Right: Lipid vacuolization in the OLETF rats.

Values with different superscripts are significantly different (p < 0.05). *Significantly different than LETO (p<0.05).

OLETF Rats Develop Hepatic Steatosis and Liver Injury

OLETF Rats Have Impaired Mitochondrial Content and Function

Daily Exercise Prevents Nonalcoholic Fatty Liver Disease

OLETF Rats Voluntarily Exercise

Daily Exercise Prevents Insulin Resistance and Type 2 Diabetes

Daily Exercise Prevents NAFLD and Loss of Mitochondrial Content and Health

CONCLUSIONS
*Findings from our interdisciplinary research group provide powerful evidence for the beneficial effects of lifestyle modifications on the treatment of obesity and nonalcoholic fatty liver disease.
*These findings have important public health application, particularly for the 60-80% of Americans who are overweight, who are physically inactive.

Supported by College of Veterinary Medicine, Department of Internal Medicine and NIH-F32DK-81952.