Western diet induced nonalcoholic steatohepatitis (NASH) in Ldlr−/− mice is only partially resolved by two separate low-fat diet regimes.

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Abstract

The prevalence of nonalcoholic fatty liver disease (NAFLD) has become a major public health concern in western societies. The progressive form of NAFLD, nonalcoholic steatohepatitis (NASH), is characterized by inflammation, oxidative stress, and fibrosis; and is a risk factor for cirrhosis and hepatocellular carcinoma. Given the scope of NASH, validating the effect of recommended treatment protocols (i.e. weight loss) is imperative. As such, we evaluated the efficacy of two separate diets: standard laboratory chow and a low-fat, low-cholesterol (LFLC) diet. Sucrose content in the LFLC diet matched the sucrose content in the Western diet (WD). We assessed the efficacy of these low fat diets to reverse NASH in WD-fed Ldlr−/− mice. Mice maintained on the WD for 24 weeks were returned to either LFLC or Chow diets for 7-8 weeks. Livers were examined for changes in histology, gene expression, and lipids. Long term WD feeding induced obesity and a robust NASH phenotype. Returning WD-fed mice to either Chow or LFLC diet readily returned body weights to levels seen in the respective controls and abrogated most gene expression markers and all plasma markers (e.g. ALT, AST, triglycerides, cholesterol, inflammatory markers, and glucose) associated with NASH. This treatment, however, failed to fully reverse hepatic steatosis and fibrosis. Feeding LFLC diet for the duration of the study independently altered body weight, liver lipids and some gene expression markers compared to Chow fed controls, demonstrating that despite low fat and cholesterol, dietary sucrose can drive changes in liver that reflect an early NAFLD phenotype. Moreover, plasma markers do not accurately reflect liver status after diet-induced liver damage has already occurred. Based on these studies, low fat-low cholesterol diets, coupled with weight loss are not sufficient to allow for full resolution of NASH.

Background

• The prevalence of diet induced NAFLD is a major U.S. public health concern. It is estimated that ~30-40% of patients with simple steatosis will progress to NASH.
• There is no optimal standard of care for treating NASH in humans. General clinical advice is weight loss and treating underlying complications (i.e. concomitant Type 2 Diabetes, high blood pressure and dyslipidemia (elevated blood cholesterol and triglycerides)
• The reversibility of NASH is not well characterized.

Figure 2: Body and Liver Weights

WD feeding induced changes in body and liver weights. Return to control diets reversed these changes. *p-value ≤ 0.05 when compared to respective control

Results

Figure 1: Approach

We assessed the efficacy of two separate low-fat low cholesterol diets to reverse pre-established NASH.

• A candidate gene approach was used to assess the degree of reversal of response of genes associated with NASH phenotype.
• Hepatic fibrosis was assessed by liver histology.
• We also assessed the impact of weight loss on alterations in major classes of hepatic lipids.

Figure 3: Metabolic Parameters

Figure 4: Hepatic Lipid Content

Figure 5: Hepatic gene expression

Figure 6: Histology

WD feeding induced increases in plasma and hepatic triglycerides, cholesterol, plasma inflammatory markers (e.g. TLR2/TLR4 activation, endotoxin, and leptin.) Return to Chow diet reversed all of these markers, however a return to LFLC reversed plasma markers but not hepatic triglycerides and cholesterol.

Conclusion

• Feeding WD (24, 29, or 32 weeks) induced a robust NASH phenotype as evidenced by alterations in lipids, gene expression markers, and fibrotic deposition.
• Reverting WD-induced NASH animals to either Chow or LFLC diets resulted in a resolution of body and liver weights, most plasma parameters and most gene expression markers, but did not resolve alterations in hepatic lipids or fibrosis.
• Based on these studies both a weight loss and diet change is not sufficient to resolve WD-induced NASH in Ldlr−/− mice.
• The LFLC diet independently induced changes in hepatic/plasma lipids and gene expression compared to the Chow diet.

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