

Encouraging findings suggest new avenues for treating liver disease in overweight Americans

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Estimates of the prevalence of liver disease suggest that one-third of the United States population has non-alcoholic fatty liver disease (NAFLD). NAFLD is now the most common cause for elevated liver function tests in the United States, a trend related to the obesity epidemic in this country. Non-alcoholic steatohepatitis (NASH), the progressive form of NAFLD, can lead to cirrhosis and all its complications. Two studies presented at the 75th Annual Scientific Meeting of the American College of Gastroenterology investigated the effectiveness of potential treatments for NASH, one assessing pentoxifylline, a well-known drug with a well-established safety profile that inhibits the release of TNF α among other mechanisms; as well as a separate analysis of pioglitazone, an insulin sensitizer, compared to vitamin E.

Pentoxifylline Improves Progressive Liver Disease NASH Compared to Placebo

Claudia O. Zein, M.D. and colleagues at the Cleveland Veterans Affairs Medical Center and the Cleveland Clinic in Cleveland, OH conducted a double-blinded, randomized, placebo-controlled trial of pentoxifylline in patients with NASH to assess improvement in levels of transaminases and improvement in histological features of NASH as measured by the NAFLD activity score (NAS). The NAS score measures disease activity and is derived from the sum of separate scores for fat, inflammation, and ballooning in the liver.

The study, "Pentoxifylline Improves Non-Alcoholic Steatohepatitis: Results of a Double-Blinded, Randomized, Placebo-Controlled Trial," found that after one year, an improvement of 30 percent or more in ALT levels from baseline was observed in a significantly higher proportion of subjects taking pentoxifylline compared to those on placebo ($p=0.02$). Additionally, a decrease of greater than 2 points in the NAS score was seen in half the pentoxifylline group versus 16 percent of those on placebo ($p=0.01$). Pentoxifylline significantly improved steatosis (fat in the liver) and inflammation, but no significant changes in ballooning were observed. A trend suggesting lack of progression of fibrosis (scar tissue in the liver) was also noted in the pentoxifylline group compared to placebo.

"There is a need for effective treatments for NASH. Previous experimental and pilot data suggesting potential benefits of pentoxifylline in NASH encouraged us to conduct this randomized, placebo controlled trial," explained Dr. Zein.

"The higher frequency of biochemical and histological improvement observed in our study among patients who received pentoxifylline compared to placebo, suggest both a reason for hope and a need for further studies," added Dr. Zein. She advises that physicians should suspect and investigate for fatty liver disease among patients who are at high risk, including those who are overweight, diabetic, or have other elements of the metabolic syndrome. "General recommendations in the management of patients with fatty [liver disease](#) include weight reduction for obese patients, and optimized management of the components of the metabolic syndrome, if present. However, there is still a need for effective medical therapeutic agents for NASH, and that is why the results of this study are so encouraging," Dr. Zein concluded.

Indiana Study Explores Changes in Adipose Tissue

Insulin Resistance in NASH

Although insulin sensitizers have been the main focus for developing new treatments for NASH, the study by Dr. Zein and another study by the NIDDK-funded NASH Clinical Research Network (NASH CRN) presented at the ACG Annual Scientific meeting in San Antonio as a late breaking abstract indicate that pathways other than [insulin resistance](#) could be used for developing effective treatments for NASH.

The investigators from the NASH CRN have recently published a paper in The New England Journal of Medicine showing significant efficacy for vitamin E (800 I.U./day) in improving liver histology in patients with NASH. In a study presented at the 2010 ACG Meeting, "Changes in Adipose Tissue Insulin Resistance Correlate with Changes in Liver Histology in NASH Patients who Participated in the PIVENS Trial," Lauren Bell, Ph.D. and colleagues from Indiana University School of Medicine have investigated whether changes in insulin resistance are responsible for the improvement in liver histology seen with vitamin E.

Non-diabetic adult patients with NASH were randomized to receive pioglitazone (a drug used in Type 2 diabetes), vitamin E, or placebo and followed after 96 weeks of treatment. Vitamin E showed statistically significant improvement in hepatic histology whereas the response to pioglitazone was favorable, but did not reach the pre-specified p-value

"Although Adipo-IR was not different from placebo in either treatment group after 96 weeks, there were trends for improvement with pioglitazone and worsening of Adipo-IR with vitamin E, suggesting that the positive effect of vitamin E on liver histology is independent of changes in [adipose tissue](#) insulin resistance," explained Dr. Bell. The mechanism by which vitamin E improves liver histology remains unknown but it is thought to be due to its intrahepatic antioxidant effects. Dr. Bell's finding that increases in Adipo-IR correlated with

worsening fibrosis, if confirmed, could be an important non-invasive test for monitoring liver fibrosis in patients with NASH.

Provided by American College of Gastroenterology

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