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Treating obesity may improve the efficacy of therapy for hepatitis C

According to a new study, obese patients chronically infected with the hepatitis C virus (HCV) and treated with combination drug therapy may have better outcomes if the underlying abnormalities caused by excessive fat tissue are corrected. Weight loss, medications to decrease insulin resistance and extending duration or dosage of therapy are strategies that may improve the efficacy of therapy.

The results of this study appear in the June 2006 issue of Hepatology, the official journal of the American Association for the Study of Liver Diseases (AASLD). Published by John Wiley & Sons, Inc., Hepatology is available online via Wiley InterScience at www.interscience.wiley.com/journal/hepatology.

HCV is one of the leading causes of chronic liver disease worldwide, affecting 3 percent of the world's population. In the U.S. alone 4.1 million people have been infected with HCV, and up to 85 percent of those are chronic carriers of the virus. Up to 70 percent of chronic carriers will go on to develop some other form of chronic liver disease, from mild liver enzyme abnormalities to cirrhosis and liver cancer. While there is no vaccine for HCV, the current optimal treatment is combination therapy with peginterferon alfa (an immune stimulant) and ribavirin (an inhibitor of viral replication). However, this will cure only 55 percent of patients. One of the risk factors for treatment failure is obesity.

Obesity itself is linked to the disruption of hormone signaling pathways that affect cell function and to abnormal levels of circulating proteins and sugars. In other words, obesity is associated with a wide range of metabolic changes that affect multiple cellular and organ functions. This biochemical disregulation is linked to serious chronic medical conditions, such as heart disease, diabetes, and non-alcoholic fatty liver disease.

Given the association between obesity and metabolic abnormalities, Michael R. Charlton, M.D. of the Division of Gastroenterology and Hepatology at the Mayo Clinic and Foundation in Rochester, MN and coauthors reviewed several mechanisms by

which obesity may interfere with the treatment of chronic HCV and recommend management strategies for obese patients.

The authors identify three possible ways by which obesity may interfere with peginterferon alpha and ribavirin activity. First, fat tissue actively secretes hormones that can modulate the immune system. Increases in fat tissue may disregulate immune pathways peginterferon targets, rendering the drug ineffective. Second, obesity causes insulin resistance which itself leads to the accumulation of fat in the liver. The greater the accumulation of fat in the liver, the greater the risk of fibrosis, or scar tissue formation, that alters liver function and blood flow, often permanently. Because HCV also causes liver cells to not respond to insulin, obesity may simply compound the problem and worsen liver disease. Third, fat tissue reduces the amount of peginterferon circulating in the body. The decreased circulation of the drug may also weaken peginterferon's stimulation of the immune system against HCV.

To address all of these mechanisms, the authors make three treatment recommendations. First, weight loss to reduce fat tissue would address all three hypothesized mechanisms. Weight loss in obese HCV patients is already associated with improved liver biopsy results and liver enzyme levels. Second, treatment with drugs that improve cellular sensitivity to insulin, such as the diabetes drugs metformin or pioglitazone, would lead to reduced fat accumulation in liver cells and might reverse disease progression. Third, increasing the dosages or the duration of combination therapy may increase circulating drug levels and improve drug efficacy.

"Treatment strategies that focus on improving underlying metabolic factors associated with poor response to combination therapy are thus more likely to overcome the low sustained viral response rates often observed in obese patients infected with HCV," conclude the authors.

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Article: "Impact of Obesity on Treatment of Chronic Hepatitis C," Michael R. Charlton, Paul J. Pockros, Stephen A. Harrison, Hepatology; June 2006 (DOI: 10.1002/hep.21239).