Management of Nonalcoholic Fatty Liver Disease

- Gastroenterologists and hepatologists at Penn Medicine have developed an approach to delay or reverse the effects of nonalcoholic fatty liver disease (NAFLD), the most common liver disease in the developed world, and the second leading indication for liver transplant listing in the United States.

NAFLD is a clinical diagnosis that includes the presence of 5% or more hepatic steatosis (as determined by liver imaging or biopsy) in the absence of secondary causes of hepatic fat accumulation, such as excessive alcohol use or other chronic liver disease. NAFLD occurs most commonly in patients who have a personal and/or family history of obesity, hypertension, hypercholesterolemia and hypertriglyceridemia, insulin resistance or diabetes mellitus. It is characterized by the accumulation of free fatty acids and triglycerides in the liver.

NAFLD is a variable disease: patients with bland steatosis may have few, if any, signs of illness. A more severe form of NAFLD, nonalcoholic steatohepatitis (NASH) involves histologic evidence of steatosis and inflammation and is a serious, progressive, and often asymptomatic condition. NASH is driven by a cascade of factors that includes systemic inflammation, insulin resistance, and oxidative stress. In its later stages, NASH may result in the development of fibrosis, cirrhosis and hepatocellular carcinoma (HCC). NASH patients with visceral adiposity and insulin resistance are at increased risk of advanced hepatic fibrosis and cirrhosis.

At Penn Gastroenterology, the objective of NAFLD management is to prevent, slow or reverse fibrosis and cirrhosis and to reduce the risk of cardiovascular comorbidities and other cancers, the major causes of death in those with metabolic syndrome.

Early diagnosis and intervention in NAFLD is critical to identify patients at high risk for NASH, cirrhosis and HCC. Thus, at Penn, patients considered susceptible to NASH or cirrhosis may be assigned a fibrosis risk score using an algorithm that combines serum markers (AST, ALT, FG, platelets, albumin) physical factors (age, BMI), imaging diagnostics (ultrasound, CT or MRI) and elastography, a non-invasive assessment of liver stiffness.

Elastography can be performed at the bedside with an ultrasound probe (fibroscan or ultrasound elastography) or by MRI, both of which are available at Penn Gastroenterology. These methods can accurately assess the amount of steatosis and fibrosis in the liver. Liver biopsy is required for patients who are considered likely to have significant fibrosis (and more specifically) steatohepatitis (NASH), a condition that has prognostic significance.

Initial therapy consists of dietary, lifestyle and behavioral modification. Patients who do not sufficiently respond to these measures are candidates for medical intervention. Medications (i.e., insulin sensitizers and vitamin E) may be administered to target the insulin resistance and oxidative stress that contribute to NASH. In addition, Penn has several ongoing research trials investigating medications that may improve NASH, including a small molecule irreversible caspase inhibitor, a modified bile acid and FXR agonist and a small molecule allosteric inhibitor of acetyl-CoA carboxylase.

Figure 1: The pathology of nonalcoholic fatty liver disease. A. Bland steatosis; B. Nonalcoholic steatohepatitis (NASH); C. Mallory bodies and ballooning hepatocytes; D. NASH with pericellular fibrosis.

CASE STUDY

Mr. S, a 69-year-old male, was referred to Penn Gastroenterology for evaluation of elevated liver enzymes. His medical history included obesity, hypertension, hyperlipidemia and coronary artery disease. His medications included amlodipine, hydrochlorothiazide, metoprolol, omega-3-fatty acids and rosuvastatin.

Mr. S was 5’10” tall and weighed 237 lbs. His BMI was 34; his BP was 140/100 and he had no physical signs of chronic liver disease. Moreover, his prior work-up was negative for serologic markers of chronic liver disease. A metabolic panel at Penn, however, found elevations in his liver enzyme profile: AST 46, ALT 84, and alkaline phosphatase 49, and a subsequent ultrasound was notable for the presence of steatosis. A NASH Fibrosure™ obtained after the consultation revealed evidence of fibrosis and severe steatosis.

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CASE STUDY  (Continued from cover)
Based on the above diagnostic studies, Mr. S was diagnosed with NAFLD, but he refused to have a liver biopsy to diagnose or rule out steatohepatitis. He was then advised to lose weight, with a weight loss goal of 10% of his current weight, and counselled to continue taking his statin as statins are generally safe in NAFLD and help reduce the risk of heart disease.

Returning to the clinic six months later, Mr. S reported that he’d tried a calorie restricted diet, but failed to lose any weight. At this time, he had a Fibroscan® which confirmed the presence of hepatic fibrosis. He was then referred to the Penn Weight Loss Management Clinic.

At his follow-up visit to the clinic a year later, Mr. S had lost approximately 20 pounds and had a notable improvement in his liver enzymes (AST 21, ALT 32, Alkaline phosphatase 41). He was advised to continue his focus on weight loss and adherence to his statin. He will continue follow-up visits to Penn Gastroenterology every 6-12 months to monitor his progress.

FACULTY TEAM
The Division of Gastroenterology at Penn Medicine is comprised of a multidisciplinary team of clinician specialists who treat a variety of digestive, liver and pancreatic disorders. Many Penn gastroenterologists and hepatologists are actively involved in clinical research, as well, pioneering advances within their fields to bring more options to the detection and management of inflammatory bowel disease, Crohn’s disease, celiac disease, gastroesophageal reflux disease and a spectrum of hepatobiliary disorders. The genetics of gastroenterological disease are a particular focus of research at Penn, as are the effects of comorbid disease and other risk factors.

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