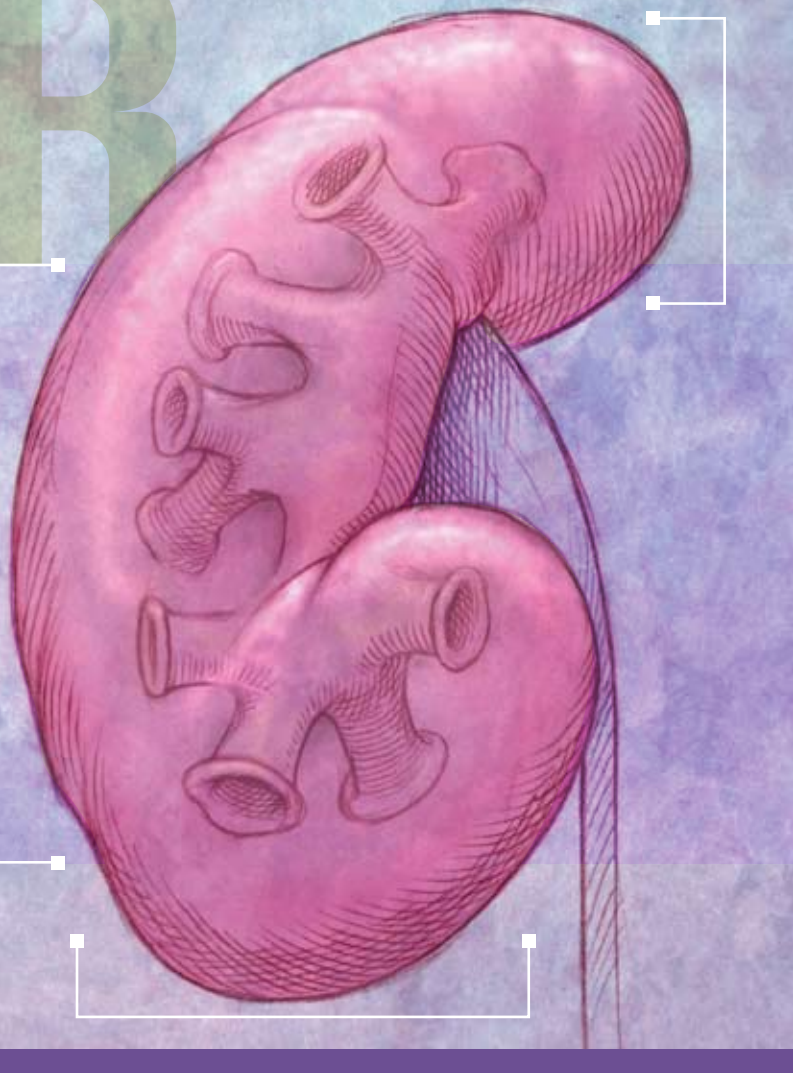
LIVER

FATTY LIVER DISEASE and NONALCOHOLIC STEATOHEPATITIS

Still Seeking Answers

by MAYU MISHINA*



Once the domain of hepatologists, non-alcoholic fatty liver disease (NAFLD) increasingly requires endocrinologist intervention due to its high incidence among patients who are obese and/or have type 2 diabetes or metabolic syndrome. With these conditions on the increase, the number of patients with fatty liver disease—or nonalcoholic steatohepatitis (NASH), an advanced stage of NAFLD—will surely escalate in coming years.

In fact, according to Kenneth Cusi, M.D., professor of medicine at the University of Texas Health Science Center in San Antonio, endocrinologists already see many patients who have NAFLD or NASH; they just don't know it. "There is not a day where a patient with NASH doesn't walk in and out of your office," Dr. Cusi said at a Meet-the-Professor presentation at **ENDO 09,** The Endocrine Society's annual meeting. "It is a lot more common than we thought before."

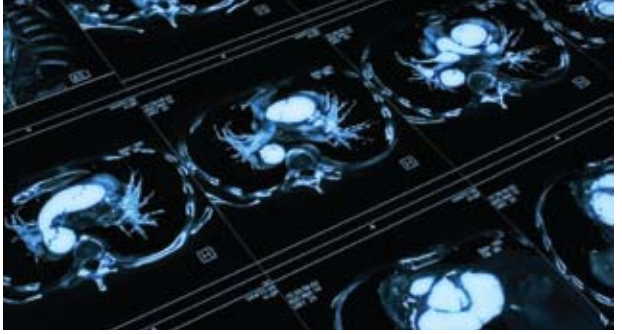
But unfamiliarity with and the lack of large, long-term studies on the disease have meant that questions currently outnumber answers. What is its natural history? How can NAFLD be diagnosed early? What causes fat in the liver to progress to the inflammation, necrosis, and fibrosis characteristic of NASH? Barring a liver biopsy, are there any effective diagnostic methods?

COMPLICATIONS with DETECTION

NAFLD is a chronic liver condition characterized by:

- Hepatic fat accumulation in the absence of ethanol abuse and other identifiable causes.
- Insulin resistance.

The disease is frequently associated with impaired glucose intolerance or type 2 diabetes, "but it's not as straightforward as you might like," said Dr. Cusi. Some obese people fall within the normal range for fatty liver, for example, whereas some lean individuals may have as much as 40% fat in their livers, whether or not they have diabetes. Patients may occasionally complain of diffuse, dull pain in their right side, but a typical exam will not yield any major findings.



Current screening based on elevated liver function tests is inadequate. High levels of liver enzymes, triglycerides, and cholesterol often hint at a fatty liver, but about 60% of patients with NAFLD show normal liver enzyme levels.

RISK for NASH

NAFLD can range from benign fat deposition in the liver to NASH, or even cirrhosis, and a critical question is how fatty liver disease progresses to NASH. In a handful of studies between 2003 and 2006, from about one-third and up to 41% of patients had developed progressive liver disease. (The disease can be reversed to some extent through diet and lifestyle intervention, currently the only accepted treatment.)

"Ethnicity is important," Dr. Cusi said. "Hispanics tend to have much more fatty liver disease than Caucasians. African Americans seem to have less fatty liver disease than Caucasians for the same degree of body mass index."

Patients with metabolic syndrome or type 2 diabetes are also at a greater risk of NASH. Other risk factors include:

- Central obesity.
- Hypertension.
- Family history of NASH.
- Severe elevation of liver transaminases.
- Older age, long-standing steatosis.
- Hepatitis C infection.

Early identification can stall disease progression to NASH, but a diagnosis can be confirmed only through a liver biopsy. All other methods involve tradeoffs. An ultrasound, for example, is "dirt-cheap" and non-invasive, said Dr. Cusi, but not very specific: "You can't determine if the patient just has benign fat sitting in the liver or is headed toward cirrhosis," he explained.

Transient elstography (Fibroscan®), a method based on ultrasound technology that measures liver stiffness (increased in cirrhosis), can rule out non-existant or minimal disease or very advanced stages of cirrhosis. But unfortunately, "most patients are in the middle," Dr. Cusi observed. A CT scan shows increased radiolucency for fibrosis and is more effective than an ultrasound—but is less affordable and more complex. Some plasma biomarkers show promise, but neither liver imaging nor blood tests have enough sensitivity or specificity. "Much more work is needed before they are validated for clinical use," he said.

NEW OPTIONS for DIAGNOSIS, TREATMENT

Thankfully, new diagnostic and treatment options are helping to change how the disease is managed. Magnetic resonance imaging with spectroscopy reportedly gives an accurate, quick, and reproducible way to quantify hepatic fat content, facilitating early NAFLD diagnosis and follow-up. However, it remains in the realm of medical research centers, like the one Dr. Cusi leads in the Diabetes Division in San Antonio.

Meanwhile, certain medications are showing positive results for fatty liver disease and NASH. Metformin has shown some efficacy, as have insulin therapy and exenatide added to insulin.

The most promising results to combat NASH have been obtained with thiazolidinediones (TZDs), which are U.S.-approved for type 2 diabetes. In the first randomized, placebo-controlled study in this area, Dr. Cusi and his colleagues showed a significant improvement in steatosis, necrosis, inflammation, and fibrosis (the latter only within the pioglitazone group, not vs. placebo) in 55 patients with NASH receiving pioglitazone for 6 months.[1] Moreover, pioglitazone improved glucose and lipid metabolism, reduced subclinical inflammation (i.e., hsCRP, TNFa, and others), and increased plasma adiponectin. In their paper,[2] the team noted that the plasma adiponectin increase was closely associated with the histological improvement during TZD therapy in patients with NASH. Comparatively, modest weight loss improved some parameters but failed to significantly reduce liver fat or improve necrosis or inflammation.

Whether TZDs are effective and safe for the long term is unclear. The drugs are contraindicated in patients with congestive heart failure grades III and IV, and doctors should monitor for lower extremity edema and potential bone loss in women.

For now, a high degree of clinician awareness may be the best method for catching and treating fatty liver disease in all its stages, Dr. Cusi said, adding, "in the near future, fatty liver disease and NASH will be screened in the same way as we currently do for retinopathy, nephropathy, and cardiovascular disease, or any other complications of type 2 diabetes." ■

* Mayu Mishina is a free-lance writer living in Silver Spring, Md.

References:

1. Belfort R, Harrison SA, Brown K, et al. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. *N Engl J Med*, 2006;355:2297–2307.
2. Gastaldelli A, Harrison SA, Belfort-Aguilar R, et al. Importance of changes in adipose tissue insulin resistance to histological response during thiazolidinedione treatment of patients with nonalcoholic steatohepatitis. *Hepatology*, 2009, Jun 9. [Epub ahead of print]. PMID: 19670459.

Causes of Fatty Liver

Factors (apart from obesity, type 2 diabetes, and metabolic syndrome) causing non-alcoholic fatty liver diseases/ conditions:

- Hepatitis C genotype 3
- Autoimmune hepatitis
- Primary biliary cirrhosis
- Alpha-1 antitrypsin deficiency
- Hepatitis B infection
- Wilson's disease
- HIV infection
- Acute fatty liver of pregnancy
- Drugs (corticosteroids, tamoxifen, diltiazem, amiodarone, methotrexate, valproic acid, antiretroviral therapy)