

## Nonalcoholic Fatty Liver Disease: An Emerging Public Health Concern

Nonalcoholic fatty liver disease (NAFLD) and the epidemic of obesity in the U.S. are closely linked. Once thought to be harmless, NAFLD is now recognized as a potentially serious illness. Research into its causes and treatments offers hope and promise for the future.

By Gina Rollins

Jimmy Cochran, 50, Stockbridge, GA, was cruising into middle age just fine – But a routine blood test revealed that all was not well. “During my annual physical, my primary care physician noticed that my liver enzymes were elevated. I have high cholesterol and was taking a medication for it. So he asked me to stop taking it for a couple of months to see if my liver enzymes straightened up. But when I went back to see him, they were even higher,” he recalls.

Cochran’s doctor realized something was amiss and sent him to a gastroenterologist. After a physical examination and liver biopsy, the GI doctor presented Cochran with startling news: He had nonalcoholic steatohepatitis (NASH), an increasingly common condition that involves the build-up of fat and inflammation in the liver. NASH is in the middle of a spectrum of illness known as nonalcoholic fatty liver disease (NAFLD). The least severe is steatosis or fatty liver, the simple accumulation of fat in the liver. NASH may progress to cirrhosis of the liver in some people. Cirrhosis entails fat build-up, inflammation and scarring in the liver. Some people with NASH may also develop liver cancer.

No longer just a curiosity

Once considered somewhat a medical curiosity, NAFLD is not recognized as a potentially serious condition. “Originally, it was thought to be not harmful, but in the last 10 years, there’s been a lot of research, and we realize it’s not a benign disease. It causes the type of liver injury under the microscope that’s very similar to the liver injury seen in alcoholics, yet people with NAFLD don’t abuse alcohol,” explains AGA member Paul Angulo, MD, associate professor of medicine at the Mayo Clinic in Rochester, Minn.

NAFLD also is quickly becoming a public health concern. “It’s linked to the epidemic of obesity in North America. If you’re overweight, you’re at risk for NAFLD, and if you’re obese, you’re at increased risk,” says AGA member Arun Sanyal, MD, chair of the division of gastroenterology, hepatology and nutrition at Virginia Commonwealth University in Richmond. Recent figure from the U.S. National Center for Health Statistics estimate the 64 percent of adults older than age 20 are overweight, and 30 percent are obese. People are considered overweight when their weight, corrected for height (also known as body mass index \_\_ BMI) is 25 or higher; obese individuals have a BMI of 30 or greater.

At fist, clinicians thought NAFLD was a condition primarily of obese women with type 2 diabetes, but they now know it affects both males and females of all ages, including children. Based on 2000 census figures, as many as 30 million American adults may have NAFLD, and up

to 8.6 million may have NASH. Simple fatty liver is present in at least one-third of obese people, and up to 80 percent of the morbidly obese, who have BMIs of 35 or higher. NAFLD affects only a small percentage of people with normal body weight.

### The Insulin Resistance Link

The cause of NAFLD is not completely clear, but virtually all who have it also have insulin resistance. Insulin is a hormone produced by the pancreas that helps the body control sugar and fat metabolism. People with insulin resistance aren't able to use insulin efficiently and their bodies produce more than normal. As a result they end up with high levels of both insulin and glucose circulating in their bodies.

Increased insulin causes more fatty acids than normal to float in the body, and eventually to accumulate in the liver. When the liver can't convert the fatty acids to energy, they stay as deposits of fat. In many people, the fat deposits don't cause an immediate problem, but in others, they expose the liver to further injury. "We don't understand the mechanism, but there's a second insult (after insulin resistance). Something else makes the live more vulnerable to inflammation and fibrosis. Right now there's no way to predict who will and won't progress," explains Dr. Angulo.

On theory is that oxidative stress, the normal tissue damage that occurs as a byproduct of metabolism, combined with genetic factors, causes some people with steatosis to develop NASH and eventually cirrhosis. Those most at risk of progressing from steatosis to NASH and cirrhosis are typically older than age 45, obese and have type 3 diabetes. Researchers estimate that between 15 and 20 percent of people with NAFLD or NASH go on to develop cirrhosis.

People with NAFLD and insulin resistance also often have Metabolic Syndrome, a cluster of problem including a side waist, high blood pressure, glucose and triglyceride levels and a low level of high density lipoprotein (HDL), the "good cholesterol." Joyce Johnson of Ridge Farm, Ill., is an example. "I fall into all those categories but high blood pressure," she reports. Johnson learned five years ago that she had NASH with the early stages of cirrhosis. Unlike many people with NAFLD or NASH, she experienced symptoms before being diagnosed. "I had a pain in my upper right side. The doctors thought it was my gallbladder, and they removed it, but the pain didn't go away. That's when they looked at my liver."

A minority of patients develop NAFLD as a result of other metabolic disorder, or from receiving total parenteral nutrition, undergoing gastric bypass surgery or taking certain medications.

### Few Early Warnings

The first time most people find out they have NAFLD or NASH is after routine blood work reveals abnormal liver enzymes. Typically the levels of these enzymes – alanine aminotransferase (ALT) and aspartate aminotransferase (AST) – are elevated, and the ratio of

ALT to AST is greater than one. In contrast, people with liver disease from alcohol abuse have levels of AST higher than ALT. A liver biopsy usually isn't necessary to diagnose steatosis or NASH, but it is helpful to determine what stage of disease is present.

Some believe that as progress from NAFLD to NASH, they are more likely to experience fatigue. "I feel like my body had been poured full of concrete," is how Pedgie Conrad of Gates, Tenn., describes the exhaustion that can accompany NASH. "I was spending 12 to 16 hours a day working, and now I sleep that much." Later in the disease process, particularly if cirrhosis develops, people may experience abdominal swelling, bruising and variceal bleeding, mental confusion and jaundice.

## Treatment Options

At this time, there's no specific treatment of NAFLD or NASH, but that doesn't mean nothing can be done. "In the absence of a clearly established treatment, our principal goal is to reduce risk factors, which is good for a variety of reasons beyond improving NAFLD or NASH," explains Dr. Sanyal. In most instances therapy focuses on reducing weight, treating insulin resistance or diabetes and protecting the liver from further injury. One of the main therapeutic options is diet and exercise, which tends to improve insulin resistance and lower the amount of fat accumulated in the liver. While there are no large clinical trials, there are reports of improvement in liver enzymes and the appearance of liver biopsies after gradual weight loss. This is particularly true when weight loss is accomplished with diet as well as exercise.

Cochran is pursuing such a strategy. "Since it hadn't been a long time since my liver enzymes were high, my doctor suggested that I change my diet and exercise more. I'm going back to see him (in about a month) to see if I've been able to reverse the damage that has been done. If my liver enzymes are still high, he said we'd look at medications." Cochran had already been watching his diet because of a high cholesterol problem, but he has since cut out refined carbohydrates and reduced his intake of dairy products and pasta.

Experts caution that while weight loss is important, it can actually worsen, NAFLD or NASH if it's not done properly. "You don't want to lose weight too fast or go on some crazy liquid diet. It will make insulin resistance worse. Weight-cycling (with large losses and gains) is also a big no-no. It hurts the liver," advises Dr. Sanyal.

A number of drug therapies are being used to treat NAFLD and NASH. Clinical trials are ongoing to determine which offer the best potential benefits. Diabetic drugs such as rosiglitazone maleate (Avandia<sup>TM</sup>), metformin HCL (Glucophage<sup>TM</sup>) and pioglitazone (Actos<sup>TM</sup>) may improve insulin resistance. Other treatments under investigation to improve liver function and to protect the liver include vitamin E, ursodeoxycholic acid (a salt normally produced by the liver in small amounts) and betaine (Cystadane<sup>TM</sup>), a nutrient that helps maintain adequate levels of protective amino acids in the liver. Cholesterol or lipid-lowering drugs like gemfibrozil also have been used.

In addition, some people with NASH are pursuing natural therapies to boost liver function. For instance, Kari Conway of Reno, Nev., takes milk thistle tablets and drinks one to two cups of green tea with honey every day. “I started studying herbs and learning about what might help,” she explains. In addition to herbal therapy, Conway changed to a low-fat diet with little red meat, lost weight and has seen her liver enzymes go down. Johnson, like many others, is hesitant to try treatments that haven’t been subjected to scientific testing. “I don’t feel comfortable adding anything like that until I have clearance from my doctor,” she explains. Her regimen involves diabetic and cholesterol-lowering medications, along with weight control and exercise.

## Finding Support

With research into the causes and treatments of NAFLD and NASH still underway, people with the disorders often find it helpful to educate themselves. “I’ve read everything on NASH, and I want to find out as much as possible,” says Conway. The unknowns and unsettling aspects of NAFLD and NASH need not be suffered in silence. “If you do research and you see something bad, take it to your doctor. Don’t be discouraged,” advises Conway. Individuals with NAFLD and NASH also find it helpful to connect with others who have the conditions either through face-to-face or virtual support groups.

In an effort to improve understanding of NAFLD and NASH the U.S. National Institute of Diabetes & Digestive & Kidney Disorders has established a clinical research network for NASH to link researchers at eight centers, coordinate data and oversee clinical trials. The goal of the network is “to answer some of the key clinical questions we don’t have answers for at this time,” according to Dr. Sanyal, who co-chairs the network. Some of its first activities include development of a registry to follow NASH patients over time and gain a better understanding of factors involved in its progression, and initiation of a clinical trial to compare three treatment approaches.

The clinical research network and other research projects offer promise for the future. “I’m very hopeful that within the next five years, we’ll have an effective treatment for NAFLD and NASH,” says Dr. Sanyal.

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Additional Resources: NAFLD/NASH Support Group: [www.liver-nash.com](http://www.liver-nash.com)

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