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## Fatty Liver: Nonalcoholic Fatty Liver Disease (NAFLD) and Nonalcoholic Steatohepatitis (NASH)

Medical Author: Michel Mendler, M.D.

Medical Editor: [Leslie J. Schoenfield, M.D., Ph.D.](#)

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### What are Fatty Liver, NAFLD, and NASH?

Nonalcoholic fatty liver disease (NAFLD) refers to a wide spectrum of liver disease ranging from simple fatty liver (steatosis), to nonalcoholic steatohepatitis (NASH), to cirrhosis (irreversible, advanced scarring of the liver). All of the stages of NAFLD have in common the accumulation of fat (fatty infiltration) in the liver cells (hepatocytes). In NASH, the fat accumulation is associated with varying degrees of inflammation (hepatitis) and scarring (fibrosis) of the liver.

The term *nonalcoholic* is used because NAFLD and NASH occur in individuals who do not consume excessive amounts of alcohol. Yet, in many respects, the histological picture of NAFLD (when we look at a biopsy piece of liver under the microscope) is similar to what can be seen in liver disease that is due to excessive intake of alcohol. As we shall see, however, the clinical circumstances in NAFLD and NASH are very different from those in alcoholic liver disease (ALD).

### What is the NAFLD spectrum?

The NAFLD spectrum is thought to begin with and progress from its simplest stage, called simple fatty liver (steatosis). That is, fatty liver is the initial abnormality in the spectrum of NAFLD. Simple fatty liver involves just the accumulation of fat in the liver cells with no inflammation or scarring. The fat is actually composed of a particular type of fat (triglyceride) that accumulates in tiny sacs within the liver cells. This accumulation of fat in liver cells is not the same as the fat cells (adipocytes) that constitute our body fat. Fatty liver is a harmless (benign) condition, which means that it, by itself, does not cause any significant liver damage.

The next stage and degree of severity in the NAFLD spectrum is NASH. Fortunately, only a fraction of patients with simple fatty liver will develop NASH. As mentioned, NASH involves the accumulation of fat in the liver cells as well as inflammation of the liver. The inflammatory cells can destroy the liver cells (hepatocellular necrosis). In the terms "steatohepatitis" and "steatonecrosis", *steato* refers to fatty infiltration, *hepatitis* refers to inflammation in the liver, and *necrosis* refers to destroyed liver cells. Strong evidence suggests that NASH, in contrast to simple fatty liver, is not a harmless condition. This means that NASH can ultimately lead to scarring of the liver (fibrosis) and then irreversible, advanced scarring (cirrhosis). Cirrhosis that is caused by NASH is the last and most severe stage in the NAFLD spectrum.

Much is not yet known about NASH and NAFLD. For example, as discussed below, the progression from each of the different stages of NAFLD is not well understood. Moreover, even liver specialists still do not agree on the exact microscopic definition of NASH. Nevertheless, individuals who develop any of the three stages of NAFLD

(fatty liver, NASH, or cirrhosis) share common risk factors. Accordingly, fatty liver and NASH are described in this article as part of the spectrum of NAFLD. Remember, NAFLD refers to the entire spectrum beginning with fatty liver, progressing through NASH, and ending with cirrhosis. NASH is that stage of the spectrum that involves fat accumulation (steatosis), inflammation (hepatitis), and scarring (fibrosis) in the liver.

### Are there other causes of fat accumulation in the liver?

Indeed, there are many other causes of fat accumulation in the liver besides NAFLD. However, NAFLD and NASH are considered the *primary* fatty liver diseases. The secondary fatty liver diseases include those that occur in other types of liver disease. Thus, alcoholic liver disease (ALD) is the most frequent secondary fatty liver disease. Secondary fatty liver can also occur in chronic [viral hepatitis C](#) (HCV), chronic viral [hepatitis B](#) (HBV), chronic autoimmune hepatitis (AIH), and Wilson's disease. (In AIH, the body's immune defense system mistakenly attacks its own liver. In Wilson's disease, an accumulation of copper injures the liver.) In all of these secondary fatty liver diseases, fatty liver is associated with other liver abnormalities distinct from NAFLD and is thought to result from liver cell injury.

Another type of secondary fatty liver disease is unrelated to other specific liver diseases. In these cases, the accumulation of liver fat is due to disturbances in the body's processing (metabolism) of fat (lipid) rather than to direct injury to the liver cells. Such causes include certain drugs (e.g., [prednisone](#)), some gastrointestinal operations (bariatric surgery) for [obesity](#), malnutrition, and genetic defects in proteins that process (metabolize) lipids. As described below, all of the secondary causes of fatty liver disease must be ruled out before attempting to establish the diagnosis of NAFLD. This is why NAFLD is considered a *diagnosis of exclusion*.

### How long have we known about NAFLD and NASH?

Liver specialists (hepatologists) actually recognized what is now called NASH in the 1970's, but it was described under different names. In 1980, Dr. J. Ludwig from the Mayo Clinic in Rochester, Minnesota made an astute observation. He noted that certain individuals who share common features (obesity, diabetes, and elevated cholesterol) had a liver disease that closely resembled alcoholic liver disease (ALD). However, these patients drank no alcohol whatsoever. So, Dr. Ludwig was the first to coin the term nonalcoholic steatohepatitis (NASH). For many years, however, NASH was thought by most doctors to be a totally harmless condition. Or, it was considered an innocent bystander that was associated with other liver diseases (especially viral hepatitis). In fact, during those years, simple fatty liver (steatosis) and NASH were considered to be equivalent processes.

The discovery of the [hepatitis C](#) virus (HCV) played an accidental role in the recognition of the clinical significance of NASH. Up until 1990, individuals who had hepatitis with signs similar to those of viral hepatitis A or B (but with negative blood tests for both) were said to have non-A-non-B viral hepatitis. Then, in 1990 the hepatitis C virus was discovered. In the years that followed, the ways by which HCV is spread ([blood transfusion](#) and intravenous drug use) and its effects on the liver were recognized. It turned out that a great majority of *non-A-non-B viral hepatitis* cases were in fact due to HCV. There remained, however, some individuals whose tests were negative for HCV as well as for other types of liver disease. Only then did researchers realize that for many of these individuals, NASH was the culprit. This realization has since led to a flurry of interest and research regarding NASH and to the understanding that it is not a harmless condition.

Clinical studies and basic research on NAFLD are still in their infancy as compared to other common liver diseases, such as ALD and HCV. As a result, we continue to have an incomplete understanding of the natural history of NAFLD. Moreover, we do not know much about the processes responsible for the progression from simple fatty liver to NASH and NASH to cirrhosis.

### How common are NAFLD and NASH and who are at risk?

The NAFLD spectrum is probably the most common disease of the liver in the United States. Although precise information on the number of cases of NAFLD and NASH is limited, estimates have been made. Moreover, information is available on which individuals are at risk to develop NAFLD and NASH.

### Why is information on the number of cases limited?

To date, no data are available on the *incidence* (number of new cases per year) of NAFLD or NASH in the United States, or anywhere else in the world for that matter. To determine the incidence of this disease, long-term studies in populations at risk will be needed. Such data collection has only just begun in several medical centers.

We do have data, however, on the *prevalence* (number of cases observed at one time) of NAFLD and NASH in cross-sections of populations at risk. Therefore, knowing which individuals are at risk is important. In this regard, a large body of evidence now supports the concept that NAFLD is associated with a condition called [insulin resistance](#), which is described in more detail below. Suffice it to say at this point that [diabetes mellitus type 2](#) (DM2) and, in addition, especially the overweight condition and obesity are the most recognizable features of insulin resistance.

### What is the BMI and how does it relate to NAFLD and NASH?

As just indicated, obesity is linked closely to NAFLD. Therefore, to get a grasp on the frequency of NAFLD and NASH and the impact of obesity on NAFLD in the population, one has to understand how obesity is defined. A calculation of the [body mass index \(BMI\)](#) is a method that can be used to determine degrees of obesity.

The BMI is calculated by dividing a person's weight in kilograms by his or her height in meters squared (kg/m<sup>2</sup>). In the non-metric system, BMI = (lbs/inches<sup>2</sup>) x 703. In adults, normal weight is defined as a BMI between 20 and

25, overweight from 25 to 30, obesity from 30 to 35, significant obesity from 35 to 40, morbid obesity from 40 to 45, super obesity from 45 to 50, and super-morbid obesity greater than 50.

In addition to the BMI method, obesity can be described according to the distribution of body fat. Fat can be distributed predominantly either to the hips (gynoid or pear-shaped) or to the abdomen (central, android, or apple-shaped). An abdominal predominance of fat is the most commonly observed type of obesity in insulin resistance. Abdominal obesity is defined in men by a waist-to-hip circumference ratio greater than 1.0 or a waist circumference greater than 40 inches (102 centimeters). In women, abdominal obesity is defined by a waist-to-hip ratio greater than 0.8 or a waist circumference greater than 35 inches (88 centimeters). In fact, simple waist measurements alone seem to be the best predictor of the type of body fat distribution that is most closely associated with insulin resistance.

The normal limits that have been established for the BMI and waist circumference are not based on considerations of appearance. Rather, they are based on the significant risk of developing complications due to being overweight (BMI-related morbidity), such as coronary artery heart disease and diabetes. In children, however, normal ranges of the BMI vary according to age and gender. Furthermore, up until the age of 16, the upper limits for the normal BMI are lower than 25. Therefore, in children, the degree of overweight is more often expressed as a percentage above ideal body weight.

### **What are the estimated numbers of cases of NAFLD and NASH?**

As could be expected, primary NAFLD is observed principally in developed countries. In these societies, a sedentary lifestyle and high calorie, sugar, and fat diets lead to DM2 and obesity.

Thus, in developed countries, the overall prevalence of NAFLD in the population is estimated to be approximately 20%, and that of NASH 3%. The prevalence of each is presumably much higher in obese and diabetic persons. The reason for this presumption is that upwards of 55% of patients with NASH have DM2 and 95% are obese. Thus, the prevalence of simple fatty liver in obese persons can be estimated to be approximately 90% and that of NASH in obese persons to be 20%. NASH is typically a disease of middle-aged overweight women with predominantly central (abdominal) fat distribution. However, there are also increasing reports of NASH related to obesity in men and even in pediatric populations.

The Center for Disease Control reports that currently, approximately one half of the US adult population is overweight (BMI>25) and one quarter of the US adult population is obese (BMI>30). Projecting the prevalence of NAFLD and NASH in the obese subpopulation to the entire population would suggest that upwards of 29 million Americans have NAFLD and 6.4 million of these persons have NASH.

These estimates, however, are very general. Another way to *guesstimate* is to study the relationship between the BMI and elevated liver enzymes (serum transaminases). You see, elevated transaminases can be caused by NAFLD in obese individuals. Thus, as compared to a normal BMI of less than or equal to 25, the risk of having elevated transaminases for men is roughly 2 times greater for a BMI of 25-30, 4 times greater for a BMI of 30-35, 5 times greater for a BMI of 35-40, and 6 times greater for a BMI greater than 40. For women, the risk is 2 times greater for a BMI of 25-30, 2.5 times greater for a BMI of 30-35, 4 times greater for a BMI of 35-40, and 5 times greater for a BMI greater than 40.

The bottom line is that currently, NAFLD is the most prevalent liver disease in the United States, representing an estimated 24% of cases of liver disease.

### **What causes NAFLD and NASH?**

The exact cause of NASH is still unknown. Strong evidence, however, supports the concept that the process common to all stages of primary fatty liver disease (NAFLD) is insulin-resistance. A number of other factors may be involved as well in causing NAFLD and NASH and in progressing through the stages of NAFLD.

### **What is insulin resistance and how does it relate to NAFLD?**

Insulin resistance is a state wherein normal signaling pathways that convey biochemical messages between insulin and its target cells are disrupted. As a result, the insulin does not exert its normal or full effects. Put another way, the body is resistant to the effects of insulin.

What does insulin normally do? Well, the pancreas secretes varying amounts of insulin during the day in response to food intake. Insulin works to maintain blood sugar ([glucose](#)) at normal levels. Thus, insulin prevents blood glucose from becoming too elevated. If insulin does not work in this way, high blood sugars and diabetes would occur. Insulin is a hormone that acts on the receptors of cells to trigger the complex biochemical reactions that control blood sugar. The cells targeted by insulin are mainly the fat cells (adipocytes), muscle cells (striated myocytes), and the liver cells (hepatocytes).

In insulin resistance, a defect in these insulin receptors causes insulin to be less effective than it normally would be. Thus, the pancreas must produce more insulin than normal in order to maintain normal blood glucose levels. Initially in this process, the increased insulin levels are sufficient to maintain normal blood glucose. In these patients, however, although the blood glucose is normal, the condition of being overweight or obesity are still clues that they are insulin resistant. At this juncture, only sophisticated blood tests (such as the euglycemic clamp test) can detect insulin resistance at the biochemical level.

As the insulin resistance progresses, even very high levels of insulin become ineffective. This degree of insulin resistance leads to elevated blood sugars and diabetes mellitus, type 2 (DM2). DM2 is usually managed by diet,

exercise, and medication (see treatment section) that increases *insulin sensitivity* (the opposite of insulin resistance). If the process proceeds unchecked, however, the pancreas can no longer secrete insulin. Then, the patients require insulin injections, which condition is referred to as *insulin-dependent DM2*. Insulin resistance and DM2 are very different from diabetes mellitus type 1 (DM1), which is also called juvenile-onset diabetes. In DM1, a defect in insulin secretion occurs early on in life and requires immediate and ongoing treatment with insulin.

Insulin resistance can also surface early in life when it is due to congenital genetic abnormalities in the insulin receptors. More often, however, as described above, it becomes evident later in life as a result of acquired obesity. A sedentary lifestyle and a diet rich in carbohydrates, sugars, and fats also promote insulin resistance. Moreover, the degree of insulin resistance increases with a greater BMI and abdominal fat (that is, big waists). Elevated lipids (LDL cholesterol and triglycerides) are also associated with insulin resistance.

Insulin resistance leads to changes in the processing (metabolism) of sugar (glucose) and fat (lipid) in the liver, muscles, and fat cells (adipocytes). The result of these changes is an increased uptake (infiltration and accumulation) of triglyceride fat into the liver cells. The triglycerides are absorbed from the diet as well as channeled from abdominal fat and peripheral muscles. These large quantities of triglyceride fat are then stored in tiny sacs (vesicles) inside the liver cells.

So, this is how a fatty liver develops. In fact, it has been shown that as the BMI increases, so does the amount of fat in the liver.

### How does insulin resistance relate to NASH?

Almost all patients with NASH are insulin resistant to some degree. However, only a minority of patients who are insulin resistant develop NASH. While an increased amount of fat in the liver may in itself lead to inflammation (see below), no evidence suggests that insulin resistance alone can lead to NASH.

### What else besides insulin resistance contributes to NASH?

The process whereby liver inflammation and death of liver tissue develop in NASH remains to be clearly explained. Several theories, however, have been advanced.

First, it is possible that the accumulation of fat in the liver alone could lead to the development of NASH. According to this theory, the large quantity of fat in the liver is thought to be a source of peroxidation (removal of electrons from molecules). Peroxidation thereby generates so-called free radicals. These free radicals then damage proteins and organelles (small structures within a cell) in the liver cells. Finally, this damage leads to cell death and/or an inflammatory cell cascade that removes the afflicted cells. In other words, the fat could be thought of as potential fuel waiting to be ignited.

However, a growing body of work in animal models of fatty liver suggests a *two-hit hypothesis*. With this theory, the *first hit* is the fatty liver (steatosis). Then, a second event, or *second hit*, leads to the development of NASH. Multiple potential second hits have been suggested.

- Small hormones (cytokines), such as *tumor necrosis factor-alpha*, which is secreted by cells and involved in inflammation, may induce cell death and even increase insulin resistance.
- Intracellular organelles (mitochondria) that provide energy to the cell may malfunction and thereby cause a decrease in cell energy and lead to cell death.
- Enzymes (cytochromes) that are involved in multiple metabolic pathways may lead to increased peroxidation and its consequences, as described above.
- Receptors in the cell nucleus that are involved in triggering the effects of insulin (*peroxisome proliferator activating receptors*, *PPAR*) may fail and thus lead to insulin resistance, inflammation of the liver, and scarring of the liver.

Finally, recent research suggests that *leptin resistance* may contribute to the development of NASH. Think of this theory as analogous to the process of insulin resistance. Leptin is a very small hormone that is secreted by the brain, fat, and stomach cells in response to eating. Its main effect is to curb the appetite. Patients with NASH have abnormally elevated levels of leptin but experience no loss of appetite. That is, they are resistant to the appetite-curbing effect of leptin. The leptin also helps control the processes of inflammation and scarring within the liver cells. Furthermore, interestingly enough, leptin also increases *insulin sensitivity*. But the fact that patients with NASH are insulin resistant supports the idea that the leptin receptors are malfunctioning.

The development of severe, irreversible scarring of the liver (cirrhosis) in NASH is even more poorly understood than the development of liver inflammation and death of liver tissue, as discussed above. Cirrhosis may simply develop over time as a result of chronic inflammation and repair, or may be due to yet a *third hit*.

As with chronic viral hepatitis and alcoholic liver disease (ALD), not all patients with NAFLD are at equal risk of developing substantial liver injury. Thus, not all diabetic and obese patients will develop a fatty liver, and not all patients with a fatty liver will develop NASH. Finally, not all patients with NASH will develop cirrhosis. This varying susceptibility of individuals to these diseases coupled with multiple disease-producing pathways suggests that the cause of primary NASH is a multi-faceted process. The cause is thought to involve altered lipid metabolism that results from environmental factors and genetic predisposition. Many more years of research will be required to fully understand the cause of NASH.

## What are the symptoms of NAFLD and NASH?

The symptoms of NAFLD and NASH are identical. They are very bland (not dramatic) and non-specific (can also be observed in other diseases). They can occur at any adult age and, in children, usually appear after 10 years of age. Actually, most patients have no symptoms. They may, however, experience occasional, vague right upper-quadrant abdominal pain (below the rib-cage on the right side). This pain characteristically is dull and aching, without a predictable pattern of occurrence. It is not an intense, sudden, and severe pain, as might occur with, for example, [gallstones](#). The [abdominal pain](#) in NAFLD and NASH is thought to be due to the stretching of the liver covering (capsule) when the liver enlarges and/or when there is inflammation in the liver.

In contrast to ALD, HBV, and HCV, symptoms of severe, acute (rapid onset) liver failure (due to intense hepatitis) are *not* observed in NAFLD or NASH. The symptoms and signs of liver failure include yellowing of the skin ([jaundice](#)), intense fatigue, loss of appetite, nausea, vomiting, and confusion.

The classic signs of insulin resistance dominate the physical exam in NAFLD and NASH. As mentioned above, obesity (especially abdominal obesity) is the most frequent finding. In addition, patients with long-standing DM2 may have complications from the [diabetes](#), such as retinopathy (abnormal blood vessels in the eye), [kidney \(renal\) failure](#), and [coronary artery heart disease](#). Elevated [blood pressure](#) (hypertension) is frequent.

Acanthosis nigricans, a dark pigmentation of the skin of the armpits and neck, can be a sign of insulin resistance and is frequently seen in children with NASH. When the liver is palpated (felt by the doctor), it usually feels normal. However, when very large amounts of fat accumulate in the liver, it can become quite large with a soft, rounded edge that can be easily felt by the doctor.

The cirrhosis stage of NAFLD usually occurs later in life (age 50 to 60 years), presumably after many years of NASH. Frequently at this stage, patients have insulin dependent DM2. (With ALD or HBV, in contrast, cirrhosis can sometimes develop over a short period of time and, therefore, occur earlier in life.) NASH patients with cirrhosis can be without symptoms (asymptomatic) if diagnosed early. However, they can have typical signs of *compensated* or *decompensated* cirrhosis.

The signs of compensated cirrhosis include a large, hardened liver, small, star-shaped vessels (spider angiomas) on the skin of the upper torso, blotchy redness on the palms (palmar erythema), whitened nails, thin silky hair, loss of body hair, prominent veins on the abdomen (abdominal collateral veins), irregular or absent menstruation in pre-menopausal women, and small testes and enlarged, sometimes painful breasts (gynecomastia) in men. The signs of decompensated cirrhosis include all the above except that the liver may be shrunken and there may be swelling of the legs ([edema](#)), accumulation of fluid in the abdomen (ascites), bleeding from veins in the esophagus (varices), and mental confusion (hepatic encephalopathy).

Fatty liver has also been described in several medical syndromes (groupings of abnormalities). For example, fatty liver occurs in polycystic ovarian syndrome, in which polycystic ovaries are associated with obesity, excessive hair (hirsutism), and insulin resistance. Congenital lipodystrophy syndromes, which are rare disorders in which the fat in the torso and extremities shifts to the abdomen, are also associated with an enlarged fatty liver.

## What are the complications of NASH?

The complications of NASH include cirrhosis (also considered the last stage of NAFLD) and primary [liver cancer](#) (hepatocellular carcinoma, HCC).

The risk of developing cirrhosis in a patient with NASH is still uncertain and varies perhaps from 8% to 15%. Up to now, very few studies have followed patients over sufficient periods of time to actually document the progression of NASH to cirrhosis. There is indirect evidence, however, that NASH can lead to cirrhosis. For example, in some patients, at the time of an initial diagnosis of NASH made by [liver biopsy](#), cirrhosis is already present, along with the usual signs of NASH.

Nonetheless, it is important to understand that in most instances when cirrhosis develops, the fatty infiltration disappears (regresses) along with the inflammation. Cirrhosis in NASH with loss of fat and inflammation is referred to as *burned-out* cirrhosis. This situation may result from less fat coming to the liver by way of the portal vein (the vessel that brings blood from the intestines to the liver). In addition, a decrease in insulin secretion (with the development of insulin dependent DM2) causes the triglyceride fats to leave the liver.

Furthermore, more and more reports indicate that at least 50% of cases of *cryptogenic* cirrhosis (cirrhosis due to unidentified causes) occur in the setting of previous long-standing obesity and/or DM2. These observations suggest that insulin-resistance, hence NASH, was often the basis of what was called cryptogenic cirrhosis. In fact, the number of liver transplantations for presumed NASH-related cirrhosis is on the rise. The high rate of recurrent NASH developing in the new livers of patients receiving liver transplants for cryptogenic cirrhosis further confirms the causal role of NASH. Finally, a study from France suggests that patients with NASH have a similar risk of developing cirrhosis as do patients with HCV. As indicated above, however, the progression to cirrhosis in NASH is thought to be slow and the cirrhosis diagnosis is typically made in patients in their sixties.

There are also reports of primary liver [cancer](#) (hepatocellular carcinoma, HCC) occurring in patients with NASH-related cirrhosis. Indeed, the incidence of HCC in NASH cirrhosis appears to be similar to that observed in HCV cirrhosis (1-2% per year). The process that causes liver cancer to form in NASH cirrhosis is unknown and has not yet been studied. HCC may develop as a result of liver repair and regrowth (hepatocellular regeneration) without any factor specifically related to NASH. Some authors, however, have suggested that insulin resistance in this situation may promote the development of liver cancer.

## How are NAFLD and NASH diagnosed?



In the absence of any specific clinical or biochemical signs, NASH remains a diagnosis that is made after excluding other causes of fatty liver and other causes of elevated liver enzymes.

The most frequent biochemical abnormality in the blood in NASH is persistent, mild to moderately elevated transaminases (ALT and AST). Transaminases are the liver enzymes that are most often elevated in the various types of hepatitis. (Remember that hepatitis refers to inflammation of the liver.) In NASH, their levels tend to fluctuate from month to month, and most often the ALT is greater than the AST. This is different from alcoholic liver disease (ALD), in which the AST is usually greater than the ALT. Indeed, this fortuitous finding often leads to initially considering the diagnosis of NAFLD or NASH. Unfortunately, however, no biochemical test or imaging procedure can differentiate simple fatty liver from NASH.

Most of the other [liver blood tests](#) (e.g., bilirubin and alkaline phosphatase) are usually normal in patients with NASH. Gamma-glutamyltranspeptidase (GGTP), however, is typically moderately elevated. Serum ferritin (a protein involved in iron storage and inflammation) can be significantly elevated, but transferrin saturation is usually normal. These iron studies suggest the presence of only mild, if any, deposition of iron in the liver (iron overload).

Abnormal biochemistry tests associated with insulin resistance include elevated total [cholesterol](#), low-density lipoprotein (LDL, the so-called *bad* cholesterol), triglycerides, and blood sugar and decreased high-density lipoprotein (HDL, the *good* cholesterol). The diagnosis of NAFLD or NASH can be considered after excluding other causes of mild elevations of transaminases, such as alcoholic liver disease, drug-induced hepatitis, chronic HBV or HCV, autoimmune hepatitis, genetic [hemochromatosis](#), alpha-1-antitrypsin deficiency, and Wilson's disease.

Drugs that can promote fatty liver (secondary NAFLD) and even features of NASH include prednisone, [amiodarone](#) (Cordarone), [tamoxifen](#) (Nolvadex), [methotrexate](#) (Rheumatrex, Trexall), and [nonsteroidal anti-inflammatory drugs](#) (NSAIDs). A difficult diagnostic situation may be encountered in patients who are taking cholesterol-lowering drugs of the *statin* type. The reason for this difficulty is that [statins](#) frequently raise transaminases without producing any significant liver injury. In this situation, NAFLD can be suspected if the ALT remains elevated long after stopping the medication. However, if the statin drug is responsible, the ALT will return to normal soon after stopping the drug. Ideally, before initiating statin therapy, liver enzymes should be determined, especially in patients at high-risk for NAFLD.

A good quality liver [ultrasound](#) can be highly sensitive (detects all fatty livers) and specific (detects only fatty livers) in diagnosing fatty liver. The classic ultrasound finding with a fatty liver is a *hyperechoic* (bright) liver. Ultrasound, however, needs a skilled operator and its sensitivity decreases with increased abdominal fat. Computerized tomography (CT) scan performs well in detecting fatty liver and can even measure the degree of fat infiltration. This technique, however, is hampered by any liver iron deposition that may be associated with NAFLD. [Magnetic resonance imaging](#) (MRI) is the overall best imaging exam for fatty liver, but also remains the most expensive. Nevertheless, no imaging procedure can in itself establish the diagnosis of NASH.

Thus, a presumptive diagnosis of NAFLD can be made in an individual based on the following criteria.

- Clinical and/or biochemical signs of insulin resistance
- Chronically (long duration) elevated ALT
- Signs of fatty liver on ultrasound
- Exclusion of other causes of elevated ALT and fatty liver

Only a liver biopsy, however, can establish a definite diagnosis and determine the severity of the condition.

#### What are the difficulties in evaluating NAFLD and NASH?

To make the diagnosis of NAFLD or NASH, the doctor must fully consider the possible role of alcohol in the patient's liver disease. This consideration requires detailed interviewing of the patient. The patient must also be honest in reporting alcohol use to the doctor. Unfortunately, this is not always the case. Moreover, the quantity of alcohol required to cause liver disease is debated. In fact, the amount varies from one study to another and from one country to another, and also varies widely according to individual rates of processing (metabolizing) the alcohol.

One *unit* of an alcoholic beverage contains 10 grams of alcohol (ethanol). A unit is roughly equivalent to one 12-ounce bottle of beer (5% alcohol), one 4-ounce glass of wine (12% alcohol), or one 1-ounce shot of hard liquor (40% alcohol). Most specialists would agree that at or above a consumption of 4 units/day in women and 6 units/day in men for at least a year, liver disease (due to alcohol) is highly likely to occur. However, there are reports that as little as 2 units/day in women and 4 units/day in men may be sufficient to promote liver disease, including fatty liver. The issue is further complicated by the possibility that in the setting of insulin resistance, even small quantities of alcohol could promote liver disease.

Studies have shown conclusively that NASH is associated with increased liver enzymes (transaminases). The importance of these elevations, however, can be somewhat overestimated because of what is referred to in statistics as an *inclusion* bias. That is, in most studies as well as in most clinical practice, only patients with persistently elevated transaminases are selected (included) for liver biopsies.

Some studies, however, have included patients for liver biopsies based on other criteria than elevated liver enzymes. These studies showed that NASH can be present on a liver biopsy in individuals with normal liver tests in up to 30% of cases of NASH. Furthermore, the degree of liver damage in NASH does not relate to (correlate with) the level of the liver enzymes. (Chronic HCV infection is another situation in which liver enzyme levels do not correlate with the severity of disease.) Moreover, a fatty liver alone can produce increased liver enzymes, even

high elevations.

Among *healthy* individuals, liver enzyme levels are significantly higher in those with a BMI greater than 23kg/m<sup>2</sup> as compared to those with a BMI less than 23kg/m<sup>2</sup>. This difference suggests that the upper limit of normal for liver enzymes should be adjusted according to the BMI.

All factors considered, NASH certainly cannot be diagnosed based just on a finding of abnormal liver enzymes and signs of a fatty liver on ultrasound. Furthermore, the exclusion of patients for liver biopsy on the basis of normal liver enzymes will invariably exclude potential cases of NASH.

#### **What are the diagnostic clues for severe NASH?**

The early identification of severe liver scarring, or cirrhosis, in NASH patients is of clinical importance because of the prognostic (outcome) information it conveys. This fact has led to several studies attempting to identify factors that predict severe liver scarring in patients with NASH and/or obesity. These studies found that patients at risk for severe scarring are most often age 50 or older, significantly obese (BMI greater than 30 kg/m<sup>2</sup>), and have DM2. Also, they often show an increase in liver enzymes (AST greater than ALT) despite the absence of alcohol use.

As already mentioned, some iron deposits in the liver (iron overload) may be associated with NAFLD or NASH. This appears to be more common at the stage of severe, irreversible liver scarring (cirrhosis). Testing for serum iron markers, however, turns out to be of little use in predicting any degree of liver scarring (fibrosis). Moreover, the predictive role of genetic markers (*HFE* mutations) of hemochromatosis (hereditary iron overload) appears questionable.

#### **What can a liver biopsy show and when should it be done?**

In order to diagnose NASH with precision and characterize its severity, there is still no substitute for performing a liver biopsy. To date, however, no consensus exists for a precise microscopic (pathological) definition of NASH or for a system to grade its severity.

The initial descriptions defined NASH, as its name would suggest, as the association of a fatty liver and inflammation, regardless of the presence of associated liver abnormalities. Such abnormalities can include destroyed liver cells (hepatocellular necrosis), scarring in different areas of the liver (sinusoidal or portal fibrosis), abnormal proteins (Mallory bodies) that deposit inside the liver cells, presumably due to peroxidation, and complex sugars that deposit in the nuclei of the liver cells (glycogenated nuclei, often seen in diabetes).

So, the initial studies on NASH included patients with simple criteria (just fatty liver and inflammation) for the diagnosis. Later, it was suggested that a fatty liver with inflammation alone (steatohepatitis) was not specific and that some degree of liver cell death (steatonecrosis) was required to diagnose NASH. The idea was that only a fatty liver with accompanying inflammation along with liver cell death represented significant disease, based on the biochemical findings and the potential to form cirrhosis.

Given these uncertainties as to what is or is not NASH, specialists in the field are now suggesting that a more descriptive approach be used. The trend is now to use a simple criterion (fatty liver) to establish the diagnosis of NAFLD, and then grade the severity of the disease according to inflammation, destruction of liver cells, scarring, and abnormal liver proteins.

Still, specialists do not agree as to when a liver biopsy should be performed. Since, as will be discussed below, no specific treatment is available for NAFLD or NASH, the result of a biopsy would not impact the patient's treatment. In other words, if an individual is obese and/or diabetic, he or she will be encouraged to lose weight by diet and exercise, regardless of the biopsy result.

On the other hand, it may be important to know whether an individual has severe NASH, especially if she or he is young. Severe NASH would indicate that the risk of developing cirrhosis later on is high. Therefore, a liver biopsy can provide important information about outcome (prognosis). It also can exclude the presence of other liver diseases. In research protocols, a liver biopsy may be required to qualify a patient for an investigational drug. Otherwise, the decision as to whether or not to biopsy the liver to diagnosis NASH in clinical practice should be made on a case-by-case basis.

#### **How are NAFLD and NASH treated?**

While the natural clinical history and the processes involved in the development of NAFLD are beginning to slowly unravel, no single truly effective treatment has been found to date. However, common sense dictates that weight loss, if overweight, and correcting elevated cholesterol, triglycerides, and blood sugar should be beneficial in NAFLD.

Yet, very little data exist on the effects of weight loss and exercise on the progression of fatty liver disease. One retrospective study (looking back in time) showed that in obese individuals with initially elevated transaminases, weight *gain* lead to a further increase in the liver enzymes. In contrast, a 10% weight loss lead to a significant decrease in the enzymes and even normal transaminases in some patients. The enzyme decrease occurred at the rate of 8% per 1% loss of body weight.

In studies of patients undergoing stomach (gastric) reduction operations for morbid obesity, substantial weight loss is accompanied by a marked reduction in transaminases and a regression of fatty liver. However, rapid weight loss in this situation can also *induce* the occurrence of a fatty liver with liver inflammation. Perhaps inflammatory cytokines (the small hormones mentioned earlier) and the fat that produce the fatty liver and

inflammation come from the body fat (adipose tissue), especially the remaining abdominal fat.

There are little published data on the use of glucose lowering (hypoglycemic) agents or lipid lowering agents in the treatment of NASH. Troglitazone (Rezulin) is a PPAR $\gamma$  (peroxisome proliferator activating receptor gamma) compound that, as indicated above, enhances the effects of insulin. The FDA, however, withdrew this drug from the market because it *caused* cases of severe liver injury (hepatotoxicity). Before the drug was withdrawn, however, a small trial of troglitazone in patients with NASH was conducted for 6 months. The study showed a significant decrease in transaminases, but only moderate improvement in microscopic (histological) severity in the liver biopsies.

Troglitazone, as does other medications in its class (thiazolidinediones), increases insulin sensitivity and perhaps decreases inflammation and scarring in the liver. A short trial with [gemfibrozil](#) (Lopid), a drug that lowers blood fats (antilipidemic agent), showed some positive effects. It lowered transaminases and serum triglycerides, but follow-up liver biopsies were not performed. A one-year trial of clofibrate (Atromid-S), another drug that lowers blood fats, however, had no positive effect whatsoever. [Metformin](#) (Glucophage), is an insulin-enhancing (sensitizing) agent used extensively to treat DM2. The drug was studied in a small series of NASH patients and showed beneficial effects on transaminases and decreased fatty infiltration in the liver. A larger trial is ongoing. Recent data also suggest that lowering cholesterol and triglycerides using medications such as statins help decrease fatty liver.

In one published trial, a one-year course of [ursodiol](#) (Actigall, Urso) in patients with NASH decreased transaminases and improved the liver biopsies. The way that this bile acid molecule works in NASH remains unclear, but it may involve effects on the immune system that decrease inflammation. But recent data cannot confirm efficacy of Actigall in treating fatty liver.

In view of the multiple processes involved in causing NASH, it may well be that many different classes of medications, as well as weight loss, will have beneficial effects. These drugs could conceivably include:

- **Insulin-sensitizing agents**, such as the two new thiazolidinediones, [pioglitazone](#) (Actos) and [rosiglitazone](#) (Avandia), and metformin (Glucophage)
- Medications that lower lipids such as [statin](#) drugs and Lopid
- **Drugs that improve blood flow**, such as [pentoxifylline](#) (Trental)

Presumably, weight loss through exercise and diet modification along with insulin-sensitizing agents will help reverse fatty infiltration of the liver. The other therapies might be beneficial in slowing the processes of inflammation and scarring. A combination of therapies will probably be the most beneficial.

#### What is the future of NAFLD and NASH?

NAFLD is probably the single most common liver abnormality in the United States. It appears to be linked directly to the growing epidemic of obesity in adults as well as in children. Thus, in a sense, NAFLD is a self-inflicted liver disease, much like alcoholic liver disease. But only a minority of patients who are obese or diabetic will develop severe liver disease and this is most likely determined genetically. In addition, increasing evidence suggests that obesity and diabetes can worsen alcoholic liver disease and liver disease due to HCV.

For these reasons, basic science researchers, liver specialists (hepatologists), nutritionists, and hormone specialists (endocrinologists) are combining their efforts to better understand and contain this process that has been recognized for only the past 30 years.

Research into the genetics of this process will reveal the pathways that lead to severe disease and help to recognize those patients most at risk. Clinical research will help us understand the natural clinical history of this process and perhaps identify predictors of outcome. Basic science research will be aimed at understanding how the disease comes about and the processes involved. This knowledge then may lead to the development of specific treatments. Currently, small trials are ongoing that involve insulin-sensitizing agents, such as metformin (Glucophage), rosiglitazone (Avandia), and pioglitazone (Actos). Other treatments with anti-oxidant effects may prove of value.

The bottom line, however, is that the single most effective treatment for obese people with NASH is to simply lose weight through diet and exercise. Unfortunately, this is no easy task in our present society, which is dominated by a sedentary lifestyle and high-calorie, high-carbohydrate, high-fat diets. With great effort, however, weight loss is achievable. Furthermore, in view of the likely role of fatty infiltration in other liver diseases, weight loss might be added on to the treatment of these other liver diseases, such as anti-viral therapy for HCV. Ultimately, NASH can probably be largely prevented and eliminated by promoting healthy eating habits and active lifestyles in children, where it all begins.

#### NAFLD and NASH At A Glance

- Accumulation of fat in the liver (fatty liver) is common to all stages of nonalcoholic fatty liver disease (NAFLD). The initial stage in the spectrum of NAFLD is simple fatty liver (steatosis).
- The basic cause of NAFLD is insulin resistance, which is a biochemical state that diminishes the effects of insulin. The most frequent risk factor for insulin resistance is obesity, especially abdominal obesity.
- Simple fatty liver is in itself quite harmless, disappears rapidly with weight loss, and only a minority of those affected progress to NASH, which is the next stage of NAFLD,
- Along with the accumulation of liver fat, NASH involves inflammation of the liver (hepatitis), destruction



(necrosis) of liver cells, and scarring (fibrosis) of the liver. It can progress to severe liver disease, including cirrhosis, which is the last stage of NAFLD.

- The risk factors, the time-line, and the processes (mechanisms) responsible for progression through the stages of NAFLD are still unknown.
- Estimates of the number of cases of NAFLD among the obese and patients with diabetes mellitus type 2 (DM2) suggest that 90% have simple fatty liver, 20% have NASH, and 10% have cirrhosis. Among those with cirrhosis, primary liver cancer develops at a rate of approximately 1% to 2% per year.
- The presumptive diagnosis of NAFLD or NASH is made in individuals who are insulin resistant, have mildly elevated liver enzymes (transaminases) in the blood, and have signs of fatty liver on an ultrasound. These patients will have no other known cause for these enzyme elevations or for the fatty liver, particularly no significant alcohol use.
- If weight loss results in a decrease or normalization of the liver enzymes, the diagnosis of NAFLD is practically assured. Only a liver biopsy, however, can confirm the diagnosis of NAFLD and NASH and determine the severity of the disease.
- Whether or not it is vital to perform a liver biopsy in suspected NAFLD or NASH is still debated among liver specialists since no specific treatments are available. A liver biopsy can exclude other liver diseases and provide information about the outcome (prognosis) of the condition.
- A liver biopsy may also provide an incentive for the patient to adopt a healthy lifestyle (diet and exercise) with the aim of losing weight. Weight loss, if overweight, and correcting elevated cholesterol, triglycerides, and blood sugar should be beneficial in NAFLD.

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