



## **Hepatitis C** **HCCAP**

### **Expanding Waistlines Results in More Fatty Liver Disease**

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Unlike many medical terms that leave people scratching their heads and wondering, "What the heck is that?" fatty liver describes exactly what the name implies – fat in the liver. More specifically, tiny globules of fat accumulate inside the liver cells. Excessive alcohol consumption is a common cause of fatty liver. But fatty liver also occurs in people who consume little or no alcohol. Thus, fatty liver is divided into two major categories: alcohol-related fatty liver and non-alcoholic fatty liver disease or NAFLD. A third category of this condition is secondary fatty liver disease, which describes fat accumulation that occurs as a result of another condition. Regardless of the cause, fatty liver is an increasingly common problem in the U.S.

#### **Alcohol-Related Fatty Liver**

As the site of alcohol metabolism, the liver is the organ most seriously damaged as a result of excessive alcohol intake. The amount of alcohol considered "excessive" often varies, depending on one's personal point of view. But from a medical standpoint, fatty liver has been shown develop in some people with as little as 10 servings\* of alcohol per week. Approximately 15 million people in the United States abuse or are dependent on alcohol. Fatty liver develops in roughly 90-100% of people with heavy alcohol use. With continued alcohol use, alcohol-related fatty liver disease often progresses to

alcoholic hepatitis and may eventually lead to alcoholic cirrhosis.

Fortunately, alcohol-related fatty liver is a reversible condition. With the elimination of alcohol, the liver typically returns to normal in as little as 2 to 4 weeks. Alcohol abstinence is essential for people with alcoholic hepatitis or cirrhosis to prevent further liver damage. Among those with cirrhosis, elimination of alcohol usually results in some reversal of alcohol-induced injury. However, the liver is unlikely to return to a completely normal state.

#### **Nonalcoholic Fatty Liver Disease (NAFLD)**

NAFLD occurs in people who consume little to no alcohol, and do not have another condition that would account for an accumulation of fat in the liver. Although there are no exact figures, many experts believe NAFLD is probably the most common liver disease in the U.S. An estimated 30 to 75 million Americans, nearly 1/4 of the population, are believed to have some form of NAFLD. Obesity is closely linked to NAFLD. As Americans' waistlines have expanded, so too has the prevalence of NAFLD.

NAFLD has three distinct stages (see Figure 1). The first stage is simple fatty liver or steatosis ("steato" refers to fat). Simple fatty liver appears to be a harmless condition. However, a portion of people with this condition progress to nonalcoholic

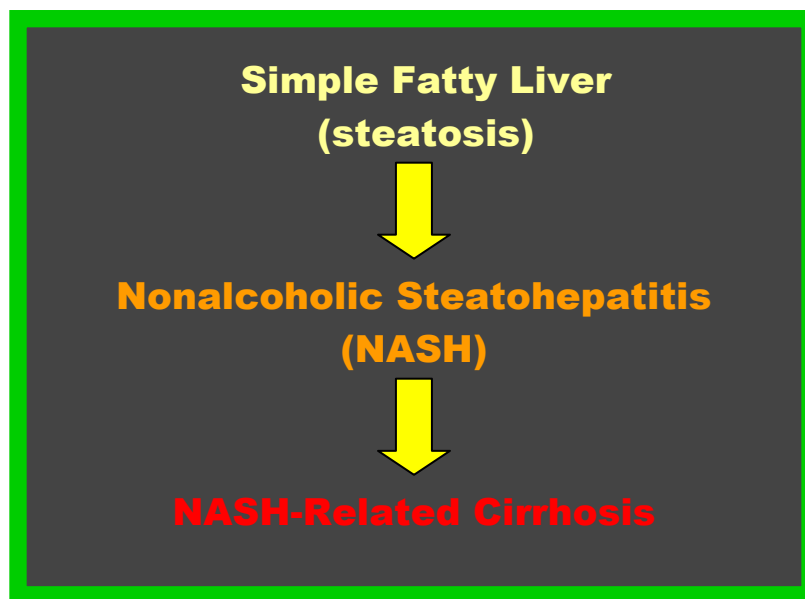
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\* A serving of alcohol is defined as one 12-ounce can of beer, one 4-ounce glass of wine, or an ounce (a shot) of hard liquor.

steatohepatitis or NASH. With NASH, the accumulation of fat is accompanied by liver inflammation (hepatitis). Over time, the inflammation present in NASH can cause liver scarring (fibrosis) in up to 40% of people with this condition. With progressive scarring, the natural structure of the liver may become distorted. This is the final stage of NAFLD known as NASH-related cirrhosis. Approximately 1/3 of people with

NASH and fibrosis develop cirrhosis within 10 years. Studies indicate that overall, 5 to 10% of people with NASH eventually develop cirrhosis. Mild forms of cirrhosis can be managed medically. However, severe cirrhosis can lead to liver failure with liver transplantation as the only treatment option. People with cirrhosis are also at increased risk for liver cancer.

**Figure 1: Spectrum of Nonalcoholic Fatty Liver Disease (NAFLD)**



Excess body weight, type 2 diabetes mellitus (adult-onset diabetes), and NAFLD are closely related. Excess body weight is commonly expressed in terms of body mass index (BMI), a measurement that takes into account both height and weight. An elevated BMI is associated with increased risk for several diseases including heart disease, adult-onset diabetes, and osteoarthritis. Some disease risks associated with excess weight are influenced by body fat distribution. Excess fat distributed predominantly in the hips is called a gynecoid or pear-shaped distribution. Excess fat carried predominantly in the gut area is

called a central or apple-shaped distribution, which is associated with an increased risk for type 2 diabetes. In turn, type 2 diabetes has been linked to an increased risk for NAFLD. The risk of NAFLD increases in parallel with the degree of obesity. In other words, as BMI increases, so does the risk of NAFLD. Evidence suggests that nearly 90% of obese persons have NAFLD, and approximately 20% have NASH. These numbers are staggering considering the fact that approximately half of the U.S. adult population is overweight, and nearly 25% are obese.

NASH is commonly diagnosed in middle-aged, overweight women with an apple-shaped fat distribution – but it is certainly not limited to those who fit this description. Early studies of NASH suggested a female predominance, but more recent studies indicate a nearly even distribution among men and women. Furthermore, NAFLD occurs in all age groups. In fact, NASH is the most common liver disease of American adolescents. This fact is certainly alarming, but it is not surprising given that obesity rates in U.S. children are skyrocketing. It is important to note that despite the strong association with obesity, NAFLD can also occur in people who are not overweight.

The exact cause of NAFLD is still being investigated. However, research to date points to insulin resistance as a key factor in the development of NAFLD. Insulin is a chemical produced by the pancreas. Its job is to maintain blood sugar levels within a fairly narrow range, around-the-clock. Liver, muscle, and fat cells are the main targets of insulin. Insulin attaches to these cells at a specific location called the insulin receptor. When insulin binds to its receptor, a complex series of events are triggered. The end result of these events is the efficient use and storage of blood sugar. Insulin resistance describes a condition of abnormally sluggish insulin receptors. The body must produce large amounts of insulin to overcome the sluggish response of the insulin receptors and prevent the blood sugar from getting too high. Insulin resistance characteristically increases with increasing body weight.

Since sugar and fat metabolism are closely related, insulin resistance also causes abnormalities in fat metabolism. Blood cholesterol, triglycerides, and other fats are typically elevated in people with insulin resistance. The accumulation of fat in the liver appears to be another consequence of

the abnormal fat metabolism associated with insulin resistance. A diet rich in sugar, other carbohydrates, and fats, and lack of exercise promote insulin resistance. Although insulin resistance appears to be a key factor in the development of NAFLD, researchers are convinced it is not the only factor. Everyone with insulin resistance does not develop NAFLD. However, virtually all people with NAFLD have some degree of insulin resistance.

Most people with simple fatty liver or NASH have no symptoms. When symptoms do occur, they are typically vague and non-specific such as occasional dull abdominal pain, fatigue, and lack of energy. NASH-related cirrhosis is associated with classic signs and symptoms of cirrhotic liver disease including loss of appetite, nausea, fatigue, jaundice, fever, and many others.

NAFLD is a “diagnosis of exclusion.” In other words, all other possible causes of liver disease must be excluded before a diagnosis of NAFLD is considered. Since symptoms are infrequent with NAFLD, it is often discovered coincidentally. Elevated liver enzymes are often the red flag, although people with simple fatty liver and NASH may have normal liver enzymes. Ultrasound, computed tomography (CT) scans, and magnetic resonance imaging (MRI) are sometimes used to detect the presence of fat in the liver. But unfortunately, there is no blood test or imaging procedure that can diagnose NAFLD with certainty. Only a liver biopsy can definitively establish a diagnosis of NAFLD, and determine the stage and severity of the disease. Nonetheless, a doctor may make a presumptive diagnosis of NAFLD without a liver biopsy. A presumptive diagnosis means the diagnosis is highly likely, but has not been confirmed. The criteria most doctors

employ to make a presumptive diagnosis of NAFLD are:

- Exclusion of all other liver diseases, including alcohol-induced liver disease.
- Liver enzymes have remained elevated over a prolonged period.
- Clinical evidence of insulin resistance is present.
  - for example, excess body weight, especially in an apple-shaped distribution
- Biochemical evidence of insulin resistance is present.
  - for example, high blood sugar, cholesterol, and/or triglycerides
- Evidence of fat in the liver on ultrasound examination.

### **Other Conditions and Practices That May Cause Fatty Liver**

Heavy alcohol use is a common cause of fatty liver disease. However, many other conditions and practices can lead to fat accumulation in the liver. Chronic liver disorders such as viral hepatitis (hepatitis B and C), autoimmune hepatitis, hemochromatosis, and Wilson's disease are often associated with steatosis. With these disorders, fatty liver is thought to result from the chronic, underlying damage taking place. In other words, the fat accumulation is the result of the pre-existing liver condition.

Conditions outside the liver can also lead to fatty liver disease. For example, gastric bypass surgery (bariatric surgery) for the treatment of obesity often causes fatty liver. Rapid weight loss, starvation, and weight cycling ("yo-yo dieting") have also been linked to fatty liver. In addition, certain medications can cause steatosis including estrogens, corticosteroids (e.g., prednisone), tetracycline, warfarin (Coumadin™), amiodarone (Cordarone™), and others. Several toxic or potentially toxic chemicals such as thallium, antimony, barium,

chromates, and borates can also cause steatosis. Finally, certain genetic disorders of metabolism can cause fat accumulation in the liver. However, the overall incidence of these disorders is low.

### **Prevention and Treatment of Fatty Liver Disease**

The best advice for avoiding fatty liver disease is:

- Avoid excessive intake of alcohol.
- Maintain a healthy body weight.
- Eat a well-balanced diet, avoiding excessive amounts of sugar, other carbohydrates, and fats.
- Exercise regularly.

This probably sounds remarkably similar to the advice your own doctor gives you to minimize your risk of heart disease, diabetes, and cancer – because it is. Remember, there are many interactions in the body. Fat metabolism, blood sugar, insulin resistance, body weight, cardiovascular health, and liver health are all interrelated. Abnormalities in one or more of these body functions invariably cause disturbances in other systems.

Treatment for secondary fatty liver disease involves treatment of the underlying condition. For example, if you have chronic hepatitis C, successful treatment of that condition is likely to cause at least partial resolution of steatosis. Similarly, if you have been on estrogen therapy and develop fatty liver disease, adjusting the dose and/or form of the hormone, or discontinuation is likely to result in resolution of the liver effects.

Presently, there is no single, proven therapy for the treatment of NAFLD. Many doctors focus on management of the related insulin-resistance conditions. The thought is that if one factor contributing to insulin-resistance is controlled, other related conditions are also

likely to improve. Therefore, obese persons are encouraged to gradually lose weight with a healthy, balanced diet. Starvation diets and other rapid weight loss schemes are discouraged as they may worsen NAFLD. Regular exercise is also encouraged. People with type 2 diabetes are treated as needed to maintain normal blood sugar levels. Those with elevated cholesterol and/or triglycerides are given dietary and lifestyle counseling, and may also be treated with prescription medications. Recently, a small study of people with NAFLD and clinical obesity found that weight loss and regular exercise led to decreased liver enzyme and insulin levels, and improved quality of life. Remarkably, these improvements were present even among those who lost only 4 to 5% of their total body weight.

Researchers continue to study NAFLD in an effort to better understand the factors that lead to its development and progression. New options are being explored to halt or reverse the NAFLD process. Until NAFLD-specific treatments are available, taking steps to improve your overall health such as maintaining a healthy body weight, exercising regularly, and eating a healthy diet is your best bet for keeping your entire body (including your liver) well.