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## **NONALCOHOLIC FATTY LIVER DISEASE** **[NAFLD]**

### **Overview**

Nonalcoholic fatty liver disease (NAFLD) describes a range of conditions that affect people who drink little or no alcohol.

The mildest type is **simple fatty liver (steatosis)**, an accumulation of fat within the liver that usually causes no liver damage. A potentially more serious type, **nonalcoholic steatohepatitis (NASH)**, is associated with liver-damaging inflammation and, sometimes, the formation of fibrous tissue. In some cases, this can progress to either cirrhosis, which causes progressive, irreversible liver scarring, or to liver cancer.

Nonalcoholic fatty liver disease affects more women than men and is found in all age groups, including children. Most often, it's diagnosed in middle-aged people who are overweight or obese, and who may also have diabetes and elevated cholesterol and triglyceride levels (hyperlipidemia).

With the increasing incidence of obesity and diabetes in Western countries, nonalcoholic fatty liver disease has become a growing problem. Although its true prevalence is unknown, some estimates suggest it may already affect as many as one-third of American adults.

Because early-stage nonalcoholic fatty liver disease rarely causes any symptoms, it's usually detected because of abnormal results of liver tests done for unrelated issues. Preferred treatments include weight loss, exercise, improved diabetes control and the use of cholesterol-lowering medications. Research is under way to develop more specific treatments.

### **Signs and symptoms**

You may not have signs and symptoms of simple fatty liver (steatosis) or nonalcoholic steatohepatitis (NASH). When symptoms do occur, they are usually vague and nonspecific and may include:

- Fatigue
- Malaise

- A dull ache in the upper right abdomen, a possible sign of an enlarged liver

At a more advanced stage, such as cirrhosis, nonalcoholic fatty liver disease may cause:

- Lack of appetite
- Weight loss
- Nausea
- Small, red spider veins under your skin or easy bruising
- Weakness
- Fatigue
- Yellowing of your skin and eyes and dark, cola-colored urine
- Bleeding from engorged veins in your esophagus or intestines
- Loss of interest in sex
- Fluid in your abdominal cavity (ascites)
- Itching on your hands and feet and eventually on your entire body
- Swelling of your legs and feet from retained fluid (edema)
- Mental confusion, such as forgetfulness or trouble concentrating (encephalopathy)

## **Causes**

It's unclear what causes nonalcoholic fatty liver disease. But many researchers believe that metabolic syndrome — a cluster of disorders that increase the risk of diabetes, heart disease and stroke — may play an important role in its development. Symptoms of metabolic syndrome include:

- Obesity, particularly around the waist (abdominal obesity)
- High blood pressure (hypertension)
- One or more abnormal cholesterol levels — high levels of triglycerides, a type of blood fat, or low levels of high-density lipoprotein (HDL) cholesterol, the so-called "good" cholesterol
- Resistance to insulin, a hormone that helps to regulate the amount of sugar in your blood

Of these, insulin resistance may be the most important trigger of simple fatty liver (steatosis) and nonalcoholic steatohepatitis (NASH). Since both conditions can remain stable for many years, causing little harm, researchers have proposed that a "second hit" to the liver may trigger a progression to cirrhosis. Possible triggers include viral infections, an accumulation of excess iron in the liver (hemochromatosis) and moderate consumption of alcohol.

It's also unclear exactly how a liver becomes fatty. The fat may come from other parts of your body, or your liver may absorb an increased amount of fat from your intestine. Another possible explanation is that your liver loses its ability to change fat into a form

that can be eliminated. But one thing's certain: The eating of fatty foods, by itself, won't produce a fatty liver.

## **Risk factors**

Although the cause of nonalcoholic fatty liver disease is unclear, the condition is associated with many risk factors. The three most important ones are closely related to the metabolic syndrome and insulin resistance:

**Overweight and obesity.** Your risk increases with every pound of excess weight. More than 70 percent of people with nonalcoholic steatohepatitis (NASH) are obese. Overweight is defined as having a body mass index between 25 and 30; obesity as having a body mass index of 30 or higher.

**Diabetes.** When your body becomes resistant to the effects of insulin or your pancreas doesn't produce enough insulin to maintain a normal blood sugar (glucose) level, it can damage many organs in your body, including the liver. Up to 75 percent of people with NASH also have diabetes.

**Hyperlipidemia.** As many as 80 percent of people with NASH have elevated cholesterol and triglyceride levels.

Other risk factors include:

**Abdominal surgery.** Operations to remove large sections of the small intestine (small bowel resection), treat obesity (gastric bypass) or bypass parts of the small intestine (jejunal bypass) often lead to rapid weight loss. Losing more than one or two pounds a week, even from dieting, may increase your risk of nonalcoholic fatty liver disease.

**Chronic infection with hepatitis C or B.** Most people with hepatitis C became infected through blood transfusions received before 1992, the year improved blood-screening tests became available. Intravenous drug use with contaminated needles is now the leading risk factor for hepatitis C. In the United States, hepatitis B is usually transmitted sexually or through contaminated needles. Long-term infection with hepatitis C slowly damages the liver, with cirrhosis developing in 20 percent of people 20 or more years after infection. The older you are when you're infected with the hepatitis C virus, the more likely you are to develop cirrhosis.

**Medications.** These include oral corticosteroids (prednisone, hydrocortisone, others), synthetic estrogens (Premarin, Ortho-Est, others) for menopause, amiodarone (Cordarone, Pacerone) for heart arrhythmias, tamoxifen (Nolvadex) for breast cancer, diltiazem (Dilacor XR, Cardizem, others) for high blood pressure, anti-retroviral drugs such as indinavir (Crixivan) for infections related to HIV/AIDS, and methotrexate (Rheumatrex, Folex), an immune-suppressing medication for rheumatoid arthritis. In rare cases, cirrhosis may result from a severe reaction to amiodarone or methotrexate.

**Other conditions.** These include Wilson's disease, a hereditary condition that affects copper levels; Weber-Christian disease, which affects nutrient absorption; and

abetalipoproteinemia, a rare congenital disorder that affects the ability to digest fat. Inherited metabolic disorders that increase the risk of cirrhosis include galactosemia, a rare disorder that affects the way the body metabolizes milk sugar (lactose), and glycogen storage diseases, which prevent glycogen, the stored form of glucose, from being formed or released when the body requires it.

## **When to seek medical advice**

If you're experiencing any of the signs and symptoms of nonalcoholic fatty liver disease — fatigue, malaise and a dull ache in your upper right abdomen — see your doctor. Make an appointment for a screening if you have risk factors for nonalcoholic fatty liver disease such as obesity, diabetes and hyperlipidemia.

## **Screening and diagnosis**

Because early-stage nonalcoholic fatty liver disease seldom causes signs and symptoms, your doctor may discover it during a routine medical examination. Many cases are detected after doctors order liver tests to monitor people taking cholesterol-lowering drugs.

Before diagnosing nonalcoholic fatty liver disease, your doctor may order blood tests for other conditions that cause liver damage, such as hepatitis B and C. He or she also will inquire about your alcohol consumption during the past five years. Excess alcohol consumption — three or more drinks a day for men and two or more drinks a day for women — can also cause fatty liver and steatohepatitis.

If your doctor suspects nonalcoholic fatty liver disease, you're likely to have certain tests, including:

**A liver-function blood test.** A damaged liver releases certain enzymes. If the test shows that these enzymes are mildly elevated, it may be a sign that you have liver damage.

**Other blood tests.** Lipid panel, thyroid function tests, fasting insulin & blood sugar & HbA1C [calculate IR with HOMA or QUICKI]

**Ultrasound (ultrasonography).** This noninvasive test uses sound waves to produce a picture of internal organs, including the liver. Abdominal ultrasound is painless and usually takes less than 30 minutes. While you lie on a bed or examining table, a technician applies a conductive gel to your abdomen and places a hand-held device (transducer) on the area, moving the transducer along your skin to locate the liver and adjacent organs. The transducer emits sound waves that are reflected from your liver and transformed into a computer-generated image.

**Computerized tomography (CT).** This test uses X-rays to produce cross-sectional images of your body.

**Magnetic resonance imaging (MRI).** Instead of X-rays, MRI creates images using a magnetic field and radio waves. Sometimes a contrast dye also may be used. The test can take from 15 minutes to an hour. You may find an MRI scan to be more uncomfortable than a CT scan. That's because you'll likely be reclining on a stretcher enclosed in a tube with very little space above you or on either side. The thumping noise the machine generates is also disturbing to some people.

**A liver biopsy.** Although other tests can provide a great deal of information about the extent and type of liver damage, a biopsy is the only way to definitively diagnose nonalcoholic fatty liver disease. In this procedure, a small sample of tissue is removed from your liver and examined under a microscope. Your doctor is likely to use a thin cutting needle to obtain the sample. Needle biopsies are relatively simple procedures requiring only local anesthesia, but your doctor may choose not to do one if you have bleeding problems or severe abdominal swelling (ascites). Risks include bruising, bleeding and infection. For high risk patients [obese, diabetic, hypertensive, AST/ALT >1, markedly elevated LFTs, s/s portal HTN or radiologic evidence of fibrosis] we generally recommend a liver biopsy.

## Complications

It's difficult to predict the course of nonalcoholic fatty liver disease in any one person. Most people with simple fatty liver (steatosis) or nonalcoholic steatohepatitis (NASH) don't develop serious liver problems. Without treatment, however, these conditions may lead to cirrhosis and liver failure in some individuals. Recent studies indicate that NASH can result in the development of fibrous tissue in the liver [fibrosis] in up to 40% of patients or cirrhosis in 5-10% of patients. It is not certain why some NASH patients will progress to this serious form of chronic liver disease while others will not. Studies report that the progression to fibrosis or cirrhosis for NASH patients is variable but can occasionally occur in less than 20 years.

## Treatment

The best treatment for you depends on the underlying cause of your nonalcoholic fatty liver disease. Preferred treatments include:

**Weight loss and exercise.** If your body mass index is above 25, a diet and exercise program may reduce the amount of accumulated fat in your liver. The most effective diet is rich in fiber and low in calories and saturated fat, with total fat accounting for no more than 30 percent of total calories. But go slowly. If you lose more than one or two pounds a week, it may lead to a worsening of liver disease. Even if you aren't overweight or obese, a healthy diet and daily physical activity may reduce inflammation, lower elevated levels of liver enzymes and decrease insulin resistance.

**Diabetes control.** Strict management of diabetes with diet, medications or insulin lowers blood sugar, which may prevent further liver damage. It also may reduce the amount of accumulated fat in your liver.

**Cholesterol control.** Controlling elevated levels of cholesterol and triglycerides with diet, exercise and cholesterol-lowering medications may help stabilize or reverse nonalcoholic fatty liver disease.

**Avoidance of toxic substances.** If you have nonalcoholic fatty liver disease — especially nonalcoholic steatohepatitis (NASH) — don't drink alcohol. Also avoid medications and other substances that can cause liver damage. Talk to your doctor about which ones to avoid.

There is no standard medical treatment specifically for nonalcoholic fatty liver disease. Several possible treatments are under investigation, but so far none has proved effective. These approaches include:

**Vitamins E and C.** Since both vitamins are antioxidants, it's thought that they may reduce liver damage caused by oxidants, unstable oxygen molecules that damage cell membranes.

**Ursodiol (Actigall).** Most commonly used to treat gallstones, this drug decreases production of bile acids, which may in theory help lower elevated levels of liver enzymes in people with liver disease. However, recent studies show no long term benefit with this medication.

**Other medications.** Researchers are studying the effects of several medications on insulin resistance and nonalcoholic fatty liver disease in people with and without diabetes. These include metformin (Glucophage, Glucophage XR), pioglitazone (Actos), rosiglitazone (Avandia) and betaine (Cystadane).

## Prevention

Your best defense against nonalcoholic fatty liver disease is to maintain a healthy weight and normal cholesterol and blood sugar levels. This strategy, along with avoiding excess alcohol and other substances that could be harmful to your liver, can help reduce your risk of liver disease.

## Complementary and alternative medicine

A number of complementary and alternative therapies — many of them herbs and nutritional supplements — are available for liver problems. Some of these therapies, such as milk thistle, have been intensively studied. Others, including the antioxidants alpha-lipoic acid (thioctic acid), vitamin E, and N-acetyl cysteine — an amino acid byproduct — are under investigation.

Some of the more well-known and studied alternative therapies include:

**Milk thistle (*Silybum marianum*).** In Europe, the herb milk thistle has been used for centuries to treat jaundice and other liver disorders. Today, scientific studies suggest that the chief constituent of milk thistle, silymarin, may aid in healing and rebuilding

the liver. Silymarin seems to stimulate the production of antioxidant enzymes that help the liver neutralize toxins. It also seems to increase the production of new liver cells and may even improve the severe scarring of cirrhosis. Milk thistle is available in capsule or alcohol-free extracts at many natural food stores and some drugstores. Check with your doctor before trying this or any other herb to make sure it won't interact with other medications you're taking.

**Omega-3 fatty acids.** Found primarily in fish such as salmon, in fish oils, in flax and flaxseed oils, and in walnuts, omega-3 fatty acids may help protect the liver.