

## **Fatty liver**

Fatty liver (also known as steatorrhoeic hepatitis or steatosis hepatis) is a reversible condition where large vacuoles of triglyceride fat accumulate in liver cells via the process of steatosis. Despite having multiple causes, fatty liver disease (FLD) can be considered a single disease that occurs worldwide in those with excessive alcohol intake and those who are obese (with or without effects of insulin resistance). The condition is also associated with other diseases that influence fat metabolism. Morphologically it is difficult to distinguish alcoholic FLD from non alcoholic FLD and both show micro-vesicular and macrovesicular fatty changes at different stages.

### **Causes**

Fatty liver is commonly associated with alcohol or metabolic syndrome (diabetes, hypertension and dyslipidemia) but can also be due to any one of many causes:

#### Metabolic

Abetalipoproteinemia, glycogen storage diseases, Weber-Christian disease, Wolman disease, acute fatty liver of pregnancy, lipodystrophy

#### Nutritional

Malnutrition, total parenteral nutrition, severe weight loss, refeeding syndrome, jejuno-ileal bypass, gastric bypass, jejunal diverticulosis with bacterial overgrowth

#### Drugs and toxins

Amiodarone, methotrexate, diltiazem, highly active antiretroviral therapy, glucocorticoids, tamoxifen, environmental hepatotoxins (e.g. phosphorus, toxic mushroom)

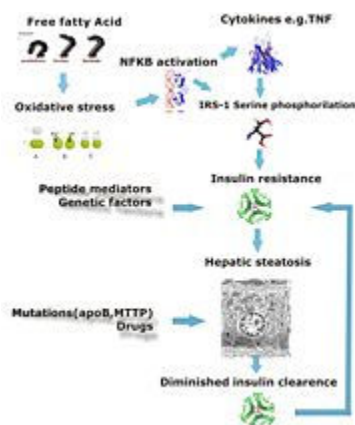
#### Other

Inflammatory bowel disease, HIV.

## Pathology

Fatty change represents the intra-cytoplasmic accumulation of triglyceride (neutral fats). At the beginning, the hepatocytes present small fat vacuoles (liposomes) around the nucleus - microvesicular fatty change. In this stage liver cells are filled with multiple fat droplets that do not displace centrally located nucleus. In the late stages, the size of the vacuoles increases pushing the nucleus to the periphery of the cell giving characteristic signet ring appearance - macrovesicular fatty change. These vesicles are well delineated and optically "empty" because fats dissolve during tissue processing. Large vacuoles may coalesce, producing fatty cysts - which are irreversible lesions. Macrovesicular steatosis is the most common form and is typically associated with alcohol, diabetes, obesity and corticosteroids. Acute fatty liver of pregnancy and Reye's syndrome are examples of severe liver disease caused by microvesicular fatty change. The diagnosis of steatosis is made when fat in the liver exceeds 5–10% by weight.

Mechanism leading to hepatic steatosis



Defects in fat metabolism are responsible for pathogenesis of FLD which may be due to imbalance in energy consumption and its

combustion resulting in lipid storage or can be a consequence of peripheral resistance to insulin, whereby the transport of fatty acids from adipose tissue to the liver is increased. Impairment or inhibition of receptor molecules (PPAR- $\alpha$ , PPAR- $\gamma$  and SREBP1) that control the enzymes responsible for the oxidation and synthesis of fatty acids appears to contribute towards fat accumulation. In addition alcoholism is known to damage mitochondria and other cellular structure further impairing cellular energy mechanism. On the other hand non alcoholic FLD may begin as excess of unmetabolised energy in liver cells. Hepatic steatosis is considered reversible and to some extent nonprogressive if there is cessation or removal of underlying cause.

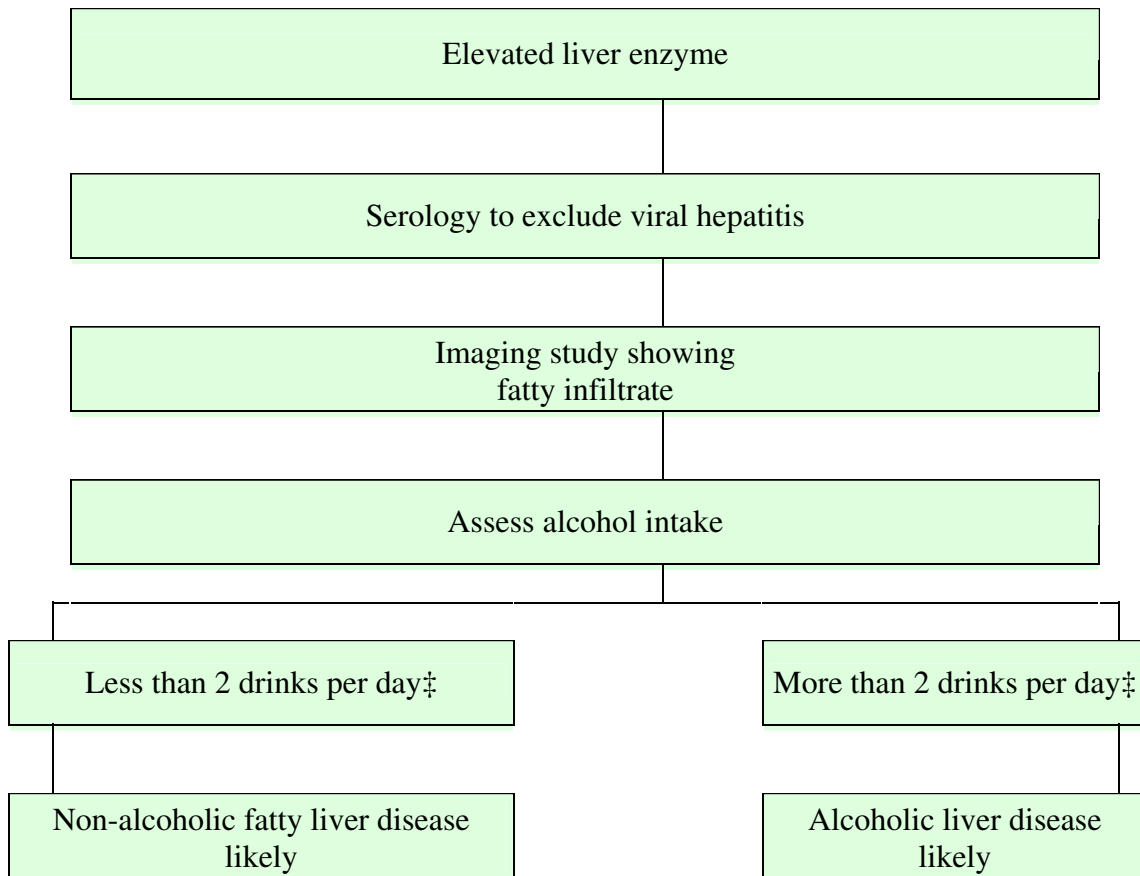
Severe fatty liver is accompanied by inflammation, a situation that is referred to as *steatohepatitis*. Progression to alcoholic steatohepatitis (ASH) or non-alcoholic steatohepatitis (NASH) depend on persistence or severity of inciting cause. Pathological lesions in both conditions are similar. However, the extent of inflammatory response varies widely and does not always correlate with degree of fat accumulation. Steatosis (retention of lipid) and onset of steatohepatitis may represent successive stages in FLD progression.

Liver with extensive inflammation and high degree of steatosis often progresses to more severe forms of the disease. Hepatocyte ballooning and hepatocyte necrosis of varying degree are often present at this stage. Liver cell death and inflammatory responses lead to the activation of stellate cells which play a pivotal role in hepatic fibrosis. The extent of fibrosis varies widely. Perisinusoidal fibrosis is most common, especially in adults, and predominates in zone 3 around the terminal hepatic veins.

The progression to cirrhosis may be influenced by the amount of fat and degree of steatohepatitis and by a variety of other sensitizing factors. In alcoholic FLD the transition to cirrhosis related to continued alcohol consumption is well documented but the process involved in non-alcoholic FLD is less clear.

## Diagnosis

### Flow chart for diagnosis modified



‡ Criteria for nonalcoholic fatty liver disease:  
consumption of ethanol less than 20g/day for woman and 30g/day for man

Most individuals are asymptomatic and are usually discovered incidentally because of abnormal liver function tests or hepatomegaly noted in unrelated medical condition. Elevated liver biochemistry is found in 50% of patients with simple steatosis. The serum ALT level usually is greater than the AST level in non-alcoholic variant and the opposite in alcoholic FLD.

Imaging studies are often obtained during evaluation process. Ultrasonography reveals a "bright" liver with increased echogenicity. A fatty liver has lower density than spleen on CT scan and fat appears bright in T1 weighted MRI. No radiological modality is however able to distinguish simple steatosis from advanced NASH.

Histological diagnosis by liver biopsy is sought when assessment of severity is indicated.

## **Treatment and prevention**

The treatment of fatty liver depends on what is causing it, and generally, treating the underlying cause will reverse the process of steatosis if implemented at early stage.

### Complication

Up to 10% of cirrhotic alcoholic FLD will develop hepatocellular carcinoma. Overall incidence of liver cancer in non-alcoholic FLD has not yet been quantified, but the association is well established.

### Epidemiology

The prevalence of FLD in the general population ranges from 10% to 24% in various countries. However, the condition is observed in up to 75% of obese people, 35% of whom will progress to non-alcoholic FLD, despite no evidence of excessive alcohol consumption. FLD is the commonest cause of abnormal liver function test in the US. African-Americans and Mexican-Americans have higher frequencies of unexplained serum aminotransferase elevations than those reported in US whites, but prevalence of FLD among different racial groups is not known.

### Signs and symptoms

Most patients with NAFLD have no or few symptoms. Infrequently, patients may complain of fatigue, malaise and dull right upper quadrant abdominal discomfort. Mild jaundice may, rarely, be noticed. More commonly NAFLD is diagnosed following abnormal liver function tests during routine blood tests. By definition, alcohol consumption of over 20 g/day (about 25ml/day) excludes the condition.

NAFLD is associated with insulin resistance and the metabolic syndrome (obesity, combined hyperlipidemia, diabetes mellitus (type II) and high blood pressure).

### Secondary causes

NAFLD can also be caused by the following medications (termed *secondary* NAFLD).

- Amiodarone
- Antiviral drugs (nucleoside analogues)
- Aspirin / NSAIDS
- Corticosteroids
- Methotrexate
- Nifedipine
- Perhexiline
- Tamoxifen
- Tetracycline
- Valproic acid

### Diagnosis

Disturbed liver enzymes are common, and liver ultrasound may show steatosis; it may also be used to exclude gallstone problems (cholelithiasis). A biopsy (tissue examination) of the liver is the only test which is widely accepted as definitively distinguishing NASH from other forms of liver disease, and can be used to assess the severity of the inflammation and resultant fibrosis.

Other tests are often carried out. Relevant blood tests include erythrocyte sedimentation rate, glucose, albumin, and renal function etc. As the liver is important in coagulation, some coagulation studies are often carried out, especially the INR (international normalized ratio). Blood tests (serology) are usually carried out to rule out viral hepatitis (hepatitis A, B, C, EBV, CMV and herpes viruses), rubella, and autoimmune causes. TSH is warranted, as hypothyroidism is more prevalent in NASH patients.

## Pathophysiology

NAFLD is considered to cover a spectrum of disease activity. This spectrum begins as fatty accumulation in the liver (hepatic steatosis). A liver can remain fatty without disturbing liver function, but by varying mechanisms and possible insults to the liver may also progress to outright inflammation of the liver. When inflammation occurs in this setting, the condition is then called NASH. Over time up to 20 percent of patients with NASH may develop cirrhosis. Cigarette smoking is not associated with an increased risk of developing NASH.

The exact cause of NAFLD is still unknown. However, both obesity and insulin resistance probably play a strong role in the disease process. The exact reasons and mechanisms by which the disease progresses from one stage to the next are the subject of much research and debate.

One debated mechanism proposes a "second hit", or further injury, enough to cause change that leads from hepatic steatosis to hepatic inflammation. Oxidative stress, hormonal imbalances and mitochondrial abnormalities are potential causes for this "second hit" phenomenon.

## Treatment

Trials to optimise treatment of NASH are being conducted (2007), and no treatment has yet emerged as the "gold standard". General recommendations include improving metabolic risk factors and reducing alcohol intake.

A large number of treatments for NAFLD have been studied. While many appear to improve biochemical markers such as alanine transaminase levels, most have not been shown to reverse histological abnormalities or reduce clinical endpoints:

- Treatment of nutrition and excessive body weight:

- Nutritional counseling: Diet changes have shown significant histological improvement.
- Weight loss: *gradual* weight loss may improve the process in obese patients; *rapid* loss may worsen NAFLD. The bad effect of rapid weight loss is controversial: the results of a meta-analysis showed that the risk of progression is very low.
- A recent meta-analysis presented at the Annual Meeting of American Association for Study of Liver Diseases(AASLD) reported that weight-loss surgery leads to improvement and or resolution of NASH in around 80 % of patients.
- Insulin sensitisers (metformin and thiazolidinediones) have shown efficacy in some studies.
- Antioxidants and ursodeoxycholic acid, as well as lipid-lowering drugs, have little benefit.

## Nonalcoholic fatty liver disease

A Mayo Clinic Report

### Introduction

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

The mildest type is simple fatty liver (steatosis), an accumulation of fat within your 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 either to cirrhosis, which can produce progressive, irreversible liver scarring, or to liver cancer.



Nonalcoholic fatty liver disease affects all age groups, including children. Most often, it is diagnosed in middle-aged people who are overweight or obese, and who may also have diabetes and elevated cholesterol and triglyceride levels.

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 affect as many as one-third of American adults.

Because early-stage nonalcoholic fatty liver disease rarely causes any symptoms, it is often detected because of abnormal results of liver tests done for unrelated issues. Treatments for nonalcoholic fatty liver disease include weight loss, exercise, improved diabetes control and the use of cholesterol-lowering medications.

### **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 your 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 hands and feet and eventually on the entire body
- Swelling of your legs and feet from retained fluid (edema)
- Mental confusion, such as forgetfulness or trouble concentrating (encephalopathy)
- Liver failure

## Causes

It is unclear exactly 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 — likely plays an important role in its development. Signs and 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 "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). Because 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 bacterial infections, hormonal abnormalities or an accumulation of excess iron in the liver caused by hemochromatosis.

It is 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 is certain: The eating of fatty foods, by itself, does not produce a fatty liver.

Researchers suspect that there may be a genetic component to the disorder, and are investigating whether genes play a role in the development of nonalcoholic fatty liver disease or if genes may affect the severity of the disorder.

### **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 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 29.9; obesity is defined 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, this can damage many organs in your body, including your liver. As many as three in four people with NASH also have diabetes.
- **Hyperlipidemia.** High cholesterol levels and elevated triglycerides are common in people who develop NASH. It is estimated that up to 80 percent of people with NASH have hyperlipidemia.

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, which may increase your risk of nonalcoholic fatty liver disease.

- **Medications.** These include oral corticosteroids (prednisone, hydrocortisone, others), synthetic estrogens (Premarin, Ortho-Est, others) for menopause, amiodarone (Cordarone, Pacerone) for heart arrhythmias, tamoxifen for breast cancer and methotrexate (Rheumatrex, Trexall), an immune-suppressing medication for rheumatoid arthritis.
- **Other conditions.** These include Wilson's disease, a hereditary condition that affects copper levels; Weber-Christian disease, which affects nutrient absorption; and a betalipoproteinemia, 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 your body requires it.

## 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 will also inquire about your current and past alcohol consumption. 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 are likely to have certain tests, including:

- **Liver-function test.** A damaged liver releases certain enzymes. If this blood test shows that these enzymes are mildly elevated, it may be a sign that you have liver damage.
- **Ultrasound (ultrasonography).** This noninvasive test uses sound waves to produce a picture of internal organs, including your 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 your 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 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 is because you will likely be reclining on a stretcher enclosed in a tube with very little space above you or beside you. The thumping noise the machine generates also is 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. Your doctor may perform this procedure if you are over age 45 and you are obese or have diabetes. Additionally, your doctor is more likely to order this test if your liver function tests do not go back to normal after treatment. 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.

## Complications

It is 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) do not develop serious liver problems. Without treatment, however, these conditions can lead to cirrhosis and liver failure in some people. This risk is highest in people older than 45 who are affected by obesity, diabetes or both. Some estimates suggest that as many as one in four people with nonalcoholic fatty liver disease may develop serious liver disease within 10 years. In some cases, a liver transplant may be the only option.

## 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. Aim to lose 10 percent of your body weight over six months, because rapid weight loss may lead to a worsening of liver disease. Even if you are not 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 may also 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) — do not drink alcohol. Also avoid medications and other substances that can cause liver damage. Talk to your doctor about which drugs to avoid.

### Under investigation

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 is 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.
- **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). Another drug being investigated is orlistat (Xenical), a medication that blocks the absorption of some of the fat from your food. Early results indicate that orlistat may reduce the amount of fat in the liver.
- **Bariatric surgery.** While abdominal weight-loss surgery coupled with rapid weight loss has been implicated as contributing to the development of NASH, some research suggests that bariatric surgery combined with modest weight loss may reduce the inflammation and scarring associated with NASH.

## **Complementary and alternative medicine**

A number of complementary and alternative therapies — many of them herbs and nutritional supplements — purport to improve liver health. Among these are milk thistle, alpha-lipoic acid (thioctic acid), vitamin E, N-acetyl cysteine (an amino acid byproduct) and omega-3 fatty acids.

Because many vitamins and dietary supplements, such as vitamin A, iron, valerian and comfrey, have the potential to worsen liver problems, be sure to check with your doctor before taking any vitamin, herb or dietary supplement.

### **Quick-burning Carbohydrate may cause Fatty Liver:**

The findings suggest that fatty liver disease -- on the upsurge among Americans as a byproduct of the obesity epidemic -- may be preventable and possibly treatable through dietary changes.

The researchers, led by David Ludwig, MD, PhD, director of the Optimal Weight for Life program at Children's Hospital Boston, fed mice either a high- or a low-glycemic index diet. High-glycemic index foods, including white bread, white rice, most prepared breakfast cereals and concentrated sugar, raise blood sugar quickly. Low-glycemic index foods, like most vegetables, fruits, beans and unprocessed grains, raise blood sugar slowly.

On the high-glycemic index diet, mice ate a type of cornstarch that is digested quickly whereas on the low-glycemic index diet, mice ate a type of cornstarch that is digested slowly. The diets had equal amounts of total calories, fat, protein, and carbohydrate, and the mice were otherwise treated identically.

After six months, the mice weighed the same. However, mice on the low-glycemic index diet were lean, with normal amounts of fat in throughout their bodies. Mice on the high-glycemic index diet had twice the normal amount of fat in their bodies, blood and livers.



When sugar melts out of high-glycemic index food, Ludwig explains, it drives up production of insulin, which tells the body to make and store fat. Nowhere is this message felt more strongly than in the liver, because the pancreas, which makes insulin, dumps the hormone directly into the liver, where concentrations can be many times higher than in the rest of the body. Fat buildup in the liver, or fatty liver, is usually symptomless, but it increases the risk for liver inflammation, which can progress to hepatitis and, in some cases, liver failure.

Fatty liver is becoming more common in Americans, especially in children, says Ludwig. Many cases in adults can be explained by alcoholism, but not the pediatric cases. Where just one case of fatty liver was reported in children in 1980, now between 1 in 4 and 1 in 2 overweight American children are estimated to have the condition. As these millions of children age, some will progress to full-blown liver disease.

"This is a silent but dangerous epidemic," says Ludwig. "Just as type II diabetes exploded into our consciousness in the 1990s, so we think fatty liver will in the coming decade."

A previous study found that Italians who ate higher-glycemic index diets had fattier livers, but the study was not tightly controlled. The new study makes clear that the type of carbohydrate can cause fatty liver in animals, independent of other elements of diet or lifestyle.

"Our experiment creates a very strong argument that a high-glycemic index diet causes, and a low-glycemic index diet prevents, fatty liver in humans," says Ludwig.

Ludwig and colleagues now hope to confirm this in a just-launched clinical trial -- and to show that a low-glycemic index diet can reverse fatty liver in overweight children. The children, aged 8 to 17, will be randomized to either the low-glycemic diet or a low-fat diet.

Low-fat diets are currently the standard treatment, Ludwig says, but many children with fatty liver do not respond to them. "We think it is

a misconception that the fat you are eating goes into the liver," he says. Ludwig hypothesizes that obesity, sedentary lifestyles and increased consumption of refined carbohydrates are "synergistically" fueling a fatty liver epidemic in children. Ironically, low-fat diets have only made matters worse, replacing fat with sugar or starchy foods that actually increase fat deposition in the body.

"Two low-fat Twinkies, billed as a health food, contain the same amount of sugar as an oral glucose tolerance test -- a test used to determine how much sugar someone can digest," Ludwig says. He notes that the French delicacy *pate de fois gras* -- the fatty liver of a duck or goose -- is produced by over-feeding the animals with high-glycemic index grains.

Researchers are looking at Vitamin E and at metformin, a drug used to treat Type II diabetes, as possible therapies for Fatty Liver Disease in 8 to 17 year olds. Fatty liver disease and signs of type 2 diabetes occurred in mice after only four weeks of a high-fat, high-sugar diet, according to a recent study. It is research that may have you thinking twice. A high-fat diet may kill regulatory T cells in the liver, allowing steatosis to develop into steatohepatitis, according to a new article. Studies in mice show that a drug used to treat diabetes, called metformin, may be helpful in combating a common and potentially fatal liver disorder. Currently, no medical treatment exists for nonalcoholic steatohepatitis (NASH), inflammation of the liver associated with the accumulation of fat in the liver.