



California Pacific
Medical Center

A Sutter Health Affiliate

With You. For Life.

Nonalcoholic Fatty Liver Disease

LIVER DISEASE MANAGEMENT & TRANSPLANT PROGRAM

At California Pacific Medical Center we are committed to bringing new and advanced diagnostic tools, medical treatments and surgical options to the physicians and patients we serve. Through this disease and treatment profile, our physicians illustrate current and emergent treatment options we can provide for the specialized medical management of your patients.

Our promise to our patients is to deliver the highest quality expert care with kindness and compassion. We go beyond medicine to treat the whole person, not just the illness.

Medicine can transform a body. Going beyond medicine can transform a life.

For patient referrals:

1-888-637-2762

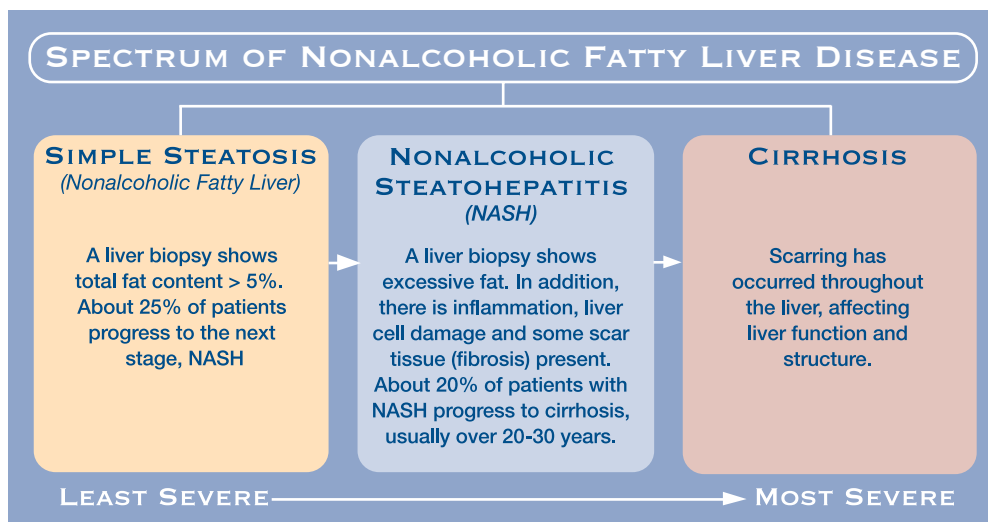
www.cpmc.org/liver

Beyond Medicine.

What is nonalcoholic fatty liver disease?

Nonalcoholic fatty liver disease (or NAFLD) is a recently recognized chronic liver disease, strongly linked to obesity. As the number of obese Americans has doubled in the past three decades, not surprisingly, NAFLD is becoming increasingly common. The hallmark of persons with NAFLD is having too much fat in the liver.

This fat is deposited within the cells of the liver (the medical term is steatosis) and this steatosis in turn can cause varying degrees of further liver injury. Importantly, while too much alcohol can also cause fat to build up in the liver, the term NAFLD refers specifically only to people with liver fat who drink little or no alcohol and therefore for whom their level of alcohol use has little to do with their liver disease.



Are there differing severities of non-alcoholic fatty liver disease?

Yes. NAFLD is an umbrella term, referring to several forms of fatty liver disease of increasing severity and importance.

- SIMPLE STEATOSIS (OR NONALCOHOLIC FATTY LIVER)** is the mildest form of NAFLD. This condition is characterized by too much fat in the liver, but without any other liver injury as a result of the fat. Simple

steatosis is often suspected when liver enzymes are elevated, and after excessive alcohol use and other liver diseases associated with fatty liver have been excluded. Often times, if the enzymes remain persistently elevated and a liver biopsy is performed, the biopsy may confirm that the total liver fat content—described as the combined small and large droplet (vesicle) fat—is greater than 5% (the upper limit of normal) and is consistent with simple steatosis. Treatment involves weight loss

through lifestyle changes. Based on our current understanding, simple steatosis is not a serious condition as it appears to rarely progress to the more severe forms of NAFLD.

■ **NONALCOHOLIC STEATOHEPATITIS (NASH)** is the next

and more serious form of NAFLD. In this case, the presence of excessive fat in the liver results in liver inflammation and further injury to the liver cells which can then lead to liver scar tissue (fibrosis) formation in some patients. At this time, the presence of NASH can only be accurately determined by examining liver tissue obtained by biopsy. Persons with NASH should be referred to a liver specialist (hepatologist) or fatty liver disease program for further management. About 20% of individuals with NASH have the potential to progress over 20-30 years to the most severe form and consequence of NAFLD: the development of NASH-related cirrhosis.

■ **NASH-RELATED CIRRHOSIS (NRC)** is the most serious form of

NAFLD and indicates scarring throughout the liver. There may or may not be residual fat in the liver. Cirrhosis can progress to liver failure resulting in the patient becoming very ill. In this case, liver transplantation may be a life-saving procedure.

How common is NAFLD?

The presence of NAFLD is strongly linked to obesity, diabetes and an associated condition called insulin resistance. It is now estimated that 20% of the adult U.S. population has simple steatosis and that 2-3% have NASH. Children can also be affected by NASH especially if they are obese.

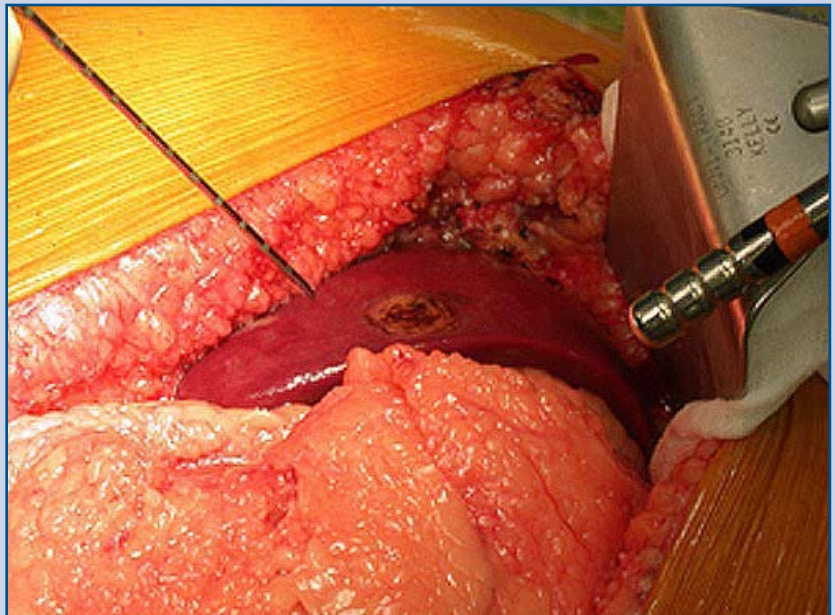
Of concern, reports are emerging of older teenagers developing NASH and even cirrhosis as a result of NASH.

Not surprisingly, cirrhosis due to NAFLD is becoming increasingly common and can progress to liver failure that may even require liver transplantation. NASH-related cirrhosis is now the third most common reason that liver transplants are performed in the U.S. It is now recognized that patients with NRC also appear to have a substantially increased risk of developing liver cancer (hepatocellular carcinoma) and therefore should be

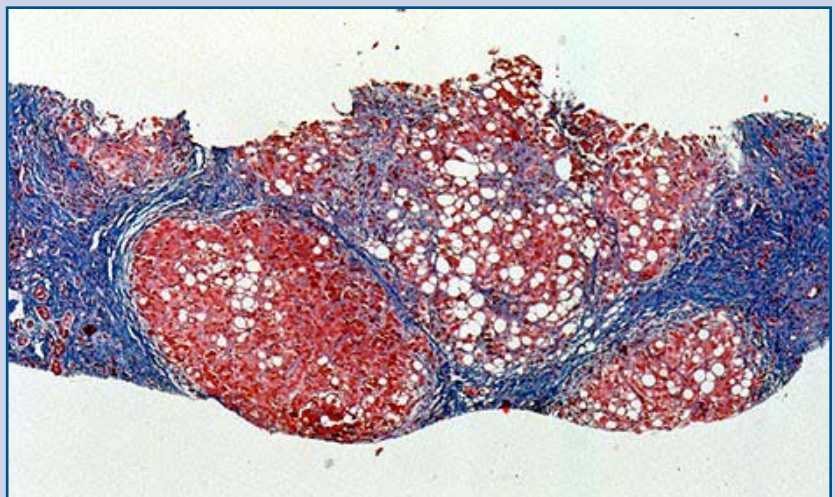
screened for this devastating complication every 6 months using an imaging study such as ultrasound or CT scan combined with a liver tumor blood marker (an alpha fetoprotein or AFP).

Why do people develop NAFLD?

People who are obese, diabetic, have high blood lipids (especially triglycerides) and high blood pressure are at greatest risk of develop-



Obese patient with fatty liver disease undergoing liver biopsy during weight loss surgery.



High-power magnification of a liver biopsy from a patient with cirrhosis due to fatty liver disease. The blue staining highlights the scar tissue.

ing NAFLD. These factors are often associated with high blood insulin levels and a reduced sensitivity of the liver and muscle to the effects of insulin—termed insulin resistance. As a result, excessive amounts of fat are deposited in the cells of the liver, often described as the “first hit.” The fat may then induce an inflammatory response within the liver—the “second hit”—leading to liver cell injury and later, to scar tissue (fibrosis) formation within the liver.

Several factors contribute to the inflammatory response in NASH. They include increased oxidative stress inside the liver cells and release of toxic inflammatory mediators (such as cytokines) by the fat cells. Genetic factors—including variation in genes controlling liver fat metabolism—are also important in the development of NAFLD.

The mechanism of liver injury in NAFLD is not completely understood. Research efforts are being pursued to study the reasons why some people develop the more severe forms of injury and to develop safe and effective means to arrest and reverse this liver damage. Also, several investigators are developing techniques to assess the presence and severity of liver injury that do not involve the need for a liver biopsy. Such methods may include new liver blood tests and liver imaging such as MRI.

What are the symptoms of NAFLD?

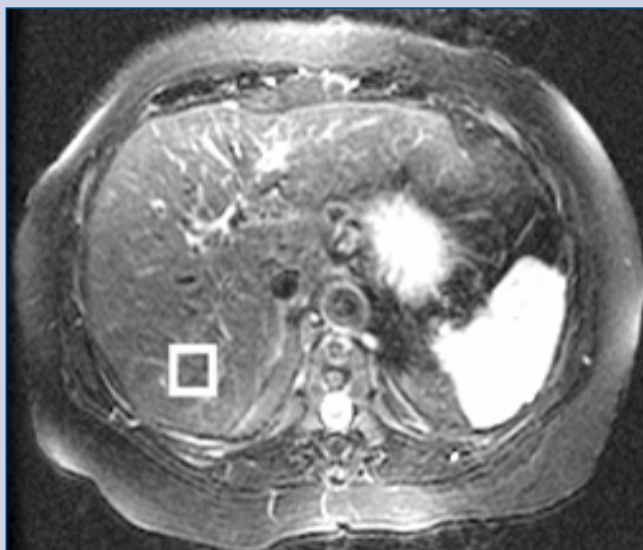
NAFLD is usually a silent disease with few or no symptoms. Some patients report an ache in the upper right side of the abdomen. Careful physical examination by a physician may demonstrate a slightly enlarged liver and acanthosis nigricans, a patchy dark discoloration of skin

especially commonly over the neck and under-arm areas. As the disease advances to cirrhosis, symptoms such as weakness, fatigue and jaundice may develop. The progression to cirrhosis can take years to decades. Cirrhosis is characterized by replacement of liver tissue by extensive scar tissue and is associated with progressive loss of liver function (the manufacture of important proteins and the clearance of toxins ingested and made as part of one’s daily metabolism). As a consequence of cirrhosis a person may develop water retention, gastrointestinal bleeding, confusion; disorientation or coma.

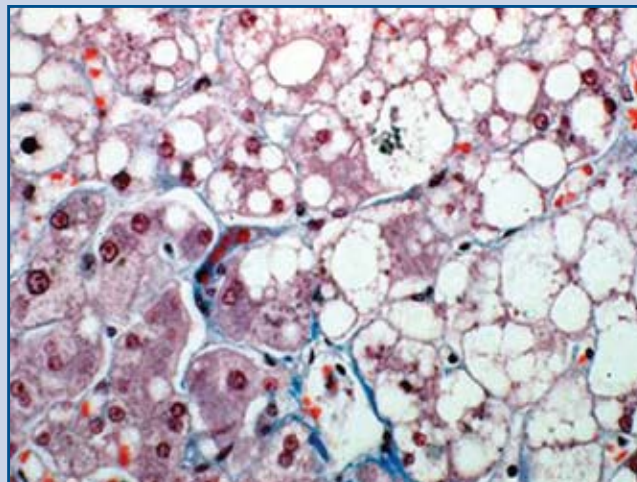
How is NAFLD diagnosed?

NAFLD is suspected when routine blood testing shows increased liver enzymes (specifically, increased AST and ALT values). An individual would then be asked about his/her alcohol use to ensure that this is not a significant factor. One’s physician may request additional blood tests to exclude other liver diseases that can also cause fat in the liver such as hepatitis C.

Unfortunately, elevated AST and ALT values do not discriminate



MRI scan of patient showing a liver (left side) with fat.



High-power magnification of a liver biopsy showing fat and inflammation in patient with nonalcoholic steatohepatitis.

between the presence of simple steatosis or the more serious NASH. As a result, referral to a liver specialist (hepatologist) may be necessary to determine the presence and severity of NASH. The hepatologist may perform other blood tests. Liver X-rays including ultrasound or CT scans may be used to confirm the presence of fat in the liver but do not help determine more important features—the amount of inflammation or scarring.

The definitive method to confirm both the presence and severity of NASH is to perform a liver biopsy. In this procedure, a very small sample of liver tissue is obtained by inserting a needle through the skin into the liver. The tissue is examined under the microscope to confirm the precise nature of NAFLD and its severity. This provides key information about the likely future progress of the condition. Currently, there are no blood tests or scans available that can reliably provide this type of information.

How is NASH treated?

As yet, there is no proven pharmacological treatment for NASH. However, there are many exciting and promising treatments currently being evaluated and new agents are anticipated within the next 12 months. It is generally recommended that patients who have NASH and are obese should try to lose weight and optimize their control of diabetes, hypertension and hyperlipidemia if present. Weight loss, especially if sustained, will improve fatty liver disease, though this is challenging in our calorie-rich environment. Gradual weight reduction (at a rate of no more than 3 pounds/week) through diet and exercise is strongly recommended. It is important to emphasize that even modest reductions in weight (5-10%) can result in

substantial reductions (~40%) in liver fat.

Many experts recommend restricting alcohol use to a limit of two drinks per day or less for men (half that for women).

The medications which appear to offer the best hope for treating NASH in preliminary studies, and perhaps not surprisingly, are those which have been used for several years to also treat diabetes. These address the fundamental metabolic abnormality in persons with NAFLD—liver resistance to the effect of insulin. These medications, called insulin sensitizers, may ultimately be used in persons with fatty liver disease, even if diabetes is not present. To confirm both their safety and efficacy, large scale clinical studies are nearing completion in evaluating these and other medications in the treatment of NASH.

Why Choose Us?

Dr. Raphael Merriman and his colleagues at California Pacific's Liver Disease Management and Transplant Program have a history and track record of expertise at the highest national and international levels in the comprehensive management of fatty liver disease. This incorporates a dedicated Fatty Liver Disease Clinic under the expert direction of Dr. Merriman—the only such clinic in Northern California. Staff at the Fatty Liver Disease Clinic work closely with California Pacific's Metabolic Center and our on-site nutritionist to outline a comprehensive treatment program for individuals with NAFLD. Physicians and their patients are offered prompt access, which facilitates the accurate assessment, diagnosis and coordinated management of all forms of fatty liver disease.

Individuals evaluated at the Fatty Liver Disease Clinic also have unparalleled access to participation in leading-edge research studies conducted at California Pacific Medical Center under

the direction of Dr. Merriman. These include the use of new medicines in carefully controlled, approved clinical studies and access to the latest research liver imaging techniques including magnetic resonance (MR) imaging and MR spectroscopy. The clinic also provides access to new research dietary interventions for NAFLD and opportunities to participate in the latest genetic and metabolic studies that address the fundamental reasons why patients develop NAFLD.

Dr. Merriman is an expert in nonalcoholic fatty liver disease with numerous research publications, book chapters and presentations at local, regional, national and international meetings on the subject. He is also a part of the National Institutes of Health, National Institute of Diabetes, Digestive and Kidney Diseases-funded NASH Clinical Research Network, which comprises of eight selected clinical centers located throughout United States focusing on innovative research in NAFLD.

For more information

Liver Disease Management & Transplant Program

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