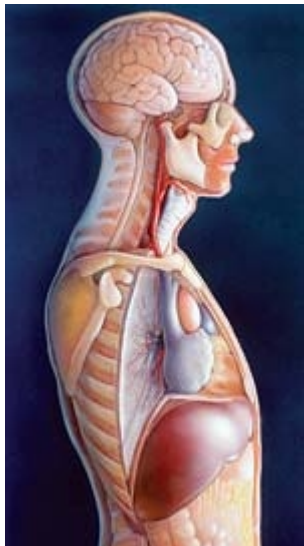


LE Magazine February 2004

REPORT

The “Hidden” Liver Disease

By Penelope Hamil



Most people take liver health for granted. After all, the liver is one of the body's most resilient organs and the only one capable of regenerating itself. Regrettably, most doctors are unaware of a liver ailment that strikes a significant portion of the population.

It is called nonalcoholic fatty liver disease. Researchers say it has become the most common liver disorder in the United States, affecting an estimated 24% of us, according to a recent study at Johns Hopkins University School of Medicine.¹ What's even more frightening is that, like diabetes and hypertension, this usually silent liver condition sneaks up and can cause life-threatening health problems years down the line.

If staying alive were easy, everyone would be doing it. People usually associate liver disorders with alcoholism or viral hepatitis. The facts reveal that nonalcoholic fatty liver disease is the villain that will most likely attack your liver

The only encouraging piece of news is that this common killer is largely preventable, and can even be reversed if caught in time. In this article, we enlighten members to the destructive effects of nonalcoholic fatty liver disease and innovative steps they can take to prevent or reverse this common hepatic disorder.

The words “nonalcoholic fatty liver disease” describe this condition well: an accumulation of fat in the liver, making up at least 10% of the organ²—in people who drink little or no alcohol. The latter distinction is an important one, say experts, because in the past, fat buildup in the liver has typically been associated with alcohol abuse. Nonalcoholic fatty liver disease is the name given to a broad spectrum of liver disease that encompasses several stages of hepatic pathologies.

Who's at Risk?

The typical person with nonalcoholic fatty liver disease is in his or her fifties, but the disease strikes people of all ages, including children.³⁻⁵ A new study finds that 65% of people over 80 years of age have nonalcoholic fatty liver disease. In this octogenarian population, gender, body weight, and lipid profile did not significantly affect the disease's incidence. The authors suggest that nonalcoholic fatty liver disease “may reach a point of being irreversible in the elderly, despite an age-associated decline in weight and lipid levels.”⁶

Nonalcoholic fatty liver disease is much more prevalent in obese and diabetic people than in the general population. An estimated 90% of obese people are at risk for the development of chronic liver injury.⁷ Moreover, about half of the estimated 16 million Americans with type II diabetes have nonalcoholic fatty liver disease.⁸ Combine obesity and diabetes, and a person's risk climbs even higher: just about all of those with both conditions have some degree of nonalcoholic fatty liver disease,⁹ almost half have nonalcoholic steatohepatitis, and 20% suffer from cirrhosis.⁸

Even more important than the fact that a person is obese is where excess fat is stored on the body. Research has shown that people who carry excess weight around their middle (abdomen or waist) are most prone to developing insulin resistance. And recent studies have revealed that the majority of people with nonalcoholic fatty liver disease have central (abdominal) obesity.^{10,11}

What's Behind the Problem?

Nonalcoholic fatty liver disease is known by its acronym, NAFLD. It is a condition characterized by steatosis (fatty liver), inflammation, insulin resistance, and the presence of fibrosis. NAFLD can evolve into cirrhosis, liver failure, and cancer.

The Three Basic Stages of Nonalcoholic Fatty Liver Disease

1. **simple fatty liver** (also called steatosis), which was formerly considered a benign condition characterized by a buildup of fat in the liver, but now has been determined to be a prognostic indicator for the treatment of hepatitis C.

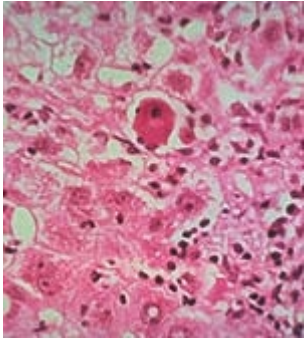
2. **nonalcoholic steatohepatitis**, in which the fatty buildup in the liver has progressed and developed inflammation (hepatitis) of the liver, as well as scarring (fibrosis).

3. **cirrhosis**, in which the scarring of the organ is advanced, irreversible, and even life threatening.

The pathogenesis of NAFLD is not well understood. Production of tumor necrosis factor-alpha (TNF-a) has been reported to be one of the early events in the many types of liver injury, and together with other TNF-a-dependent cytokines (inflammatory messengers), it may mediate a process of chronic liver injury.

During chronic liver injury, proliferation and migration of activated hepatic stellate cells are involved in the pathogenesis of hepatic fibrosis. Recent studies have demonstrated that oxidative stress stimulates production of collagen, which drives the development of fibrosis. Hepatic stellate cells are the main source of the abnormal collagen-derived extracellular matrix material that represents the biochemical hallmark of the disease process.

In recent years, a nutrient called polyenylphosphatidylcholine (PPC), a polyunsaturated phospholipid extract from soybean that inhibits stellate cell proliferation, has emerged as a promising agent for the treatment and prevention of liver cirrhosis and steatosis.¹²



Hepatitis, inflammation of the liver, showing disarray of the hepatocytes or liver cells.

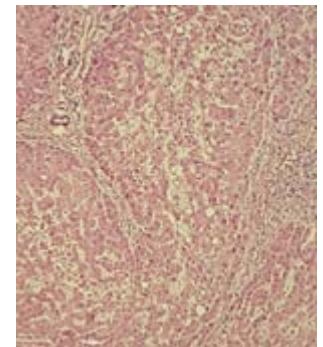
Dyslipidemia (high LDL and triglycerides; low HDL), insulin resistance, and other components of the metabolic syndrome (see sidebar, on p.56, "The Syndrome X Connection") increasingly are recognized as being associated with NAFLD. Adding weight to the theory that insulin resistance plays a leading role in the development of a fatty liver is that high insulin levels have been shown to block the oxidation (burning off) of fat in liver cells (hepatocytes), contributing to the buildup of harmful fatty acids and triglycerides in the organ.¹³⁻¹⁵ In fact, triglyceride fat is the very type of fat stored in tiny sacs inside a fatty liver.⁷ High concentrations of fatty acids (which help produce the triglycerides that can build up in the liver) are not only toxic to liver cells, but also may be directly tied to the oxidative stress that leads to the inflammation and scarring in the second stage of NAFLD.^{13,16} A recent study shows that 58% of patients with severe hypertriglyceridemia had elevated liver enzymes indicative of nonalcoholic steatohepatitis.¹⁷ Intriguingly, as we will see later, PPC has shown potent triglyceride reductions in human clinical studies.

A new study shows that insulin resistance is associated not merely with NAFLD, but with its more serious form, nonalcoholic steatohepatitis. The study employed a measure of insulin resistance known as the homeostatic model assessment (HOMA), which is calculated as the fasting insulin level times the fasting glucose level, divided by 405 (for blood tests reported in US numerical units; for European numerical units, divide by 22.5 instead of 405). A HOMA level greater than 2.2 indicates insulin resistance. Patients with simple fatty liver (steatosis) had an average HOMA level of 1.61, whereas patients with nonalcoholic steatohepatitis averaged 3.67 and were therefore insulin resistant.¹⁸ As noted earlier, dyslipidemia, including elevation of triglyceride levels, insulin resistance, and other components of the metabolic syndrome increasingly are recognized as being associated with NAFLD.

Signs, Symptoms, and Complications

Most people with NAFLD have no obvious symptoms, even when the disease has progressed to non-alcoholic steatohepatitis.⁸ Doctors report that in some cases, patients may raise very bland or general complaints such as fatigue and malaise that could be attributed to any number of common ailments. A minority of people with NAFLD may experience an occasional sensation of fullness or a vague, dull pain on the right side of the abdomen, just below the rib cage.

If the disease progresses to the more-advanced cirrhosis stage, however, a patient can suffer any number of symptoms, including blotchy red palms, prominent veins on the abdomen, star-shaped spider veins on the upper torso, thinning hair, swelling of the legs (edema), abdominal fluid retention (ascites), and even mental confusion, as well as irregular or absent menstrual periods in premenopausal women and enlarged breasts (gynecomastia) in men.⁷ Studies show that as many as 20% of patients with nonalcoholic steatohepatitis may progress to cirrhosis within a 10-year period,^{19,20} and 3% may progress to liver failure, eventually requiring liver transplantation.²¹ Because cirrhosis is typically diagnosed so late in NAFLD patients compared to those with other chronic liver diseases, it is more likely to be fatal.²² And compared to simple fatty liver sufferers, patients with advanced nonalcoholic steatohepatitis are more than 10 times more likely to die from the disease.^{23,24}



Micrograph of tissue showing cirrhosis of the liver, in which fibrous septa (membranes) divide the hepatic parenchyma into nodules and regenerative nodules develop in the surrounding hepatocytes.

Most worrisome is mounting evidence that nonalcoholic steatohepatitis can progress to hepatocellular cancer (liver cancer). A new study finds that Ki-67 staining, a marker of liver cell proliferative activity, is virtually absent in the normal liver but is seen in 54% of fatty liver patients and in 100% of nonalcoholic steatohepatitis patients. In nonalcoholic steatohepatitis, the Ki-67 index correlates with grades of necro-inflammation in the liver.²⁵

How Is NAFLD Diagnosed?

Because NAFLD is usually asymptomatic, a doctor generally will first suspect NAFLD when liver function tests during

routine blood work show that a patient's liver enzymes (in particular, alanine aminotransferase, or ALT) are mildly to moderately elevated. Studies show that as many as 29% of adults fall into this category.⁴³ But because people who do not have NAFLD may have elevated ALT levels, and because the disease also may be present whether or not a person has elevated enzyme levels⁴⁴—NAFLD is found in as many as 30% of people with normal ALT levels⁴⁵—further laboratory testing is always necessary.

The next step in the diagnosis process usually is to screen the liver by ultrasound (sonography), which uses harmless sound waves to show images of the organ. When a large amount of fat has accumulated in the liver, it may show up as enlarged and will appear “brighter” than the kidneys on the ultrasound screen;⁴⁶ however, moderate amounts of fat may not be detected by an ultrasound screening. A computed tomography (CT) or magnetic resonance imaging (MRI) scan also may be used, but most doctors opt for ultrasound, as it is less expensive and does not expose the patient to radiation. Although these tests can suggest that a patient has NAFLD—mainly by excluding other liver diseases and conditions (such as biliary tract disease and focal liver disease) that also can elevate levels of liver enzymes—they cannot give a definitive diagnosis or determine the stage of the disease.^{33,47,48}

The only way to confirm a diagnosis of NAFLD—and to gauge the severity of inflammation, fibrosis, or cirrhosis—is a liver biopsy,^{33,3,21} in which a needle is inserted into the liver to remove a sample of tissue that is then examined under a microscope. (In a fatty liver, numerous large round white sacs, or fat vacuoles, will be visible to the lab technician.) Yet many doctors are reluctant to recommend biopsy as a mean of diagnosing or assessing the degree of NAFLD, because like any surgical procedure, it carries the risk of complications, including bleeding and infection. Moreover, as there is no proven specific treatment for the disease, having a definitive diagnosis via biopsy is not very likely to affect the management of the disease in a particular patient.⁴⁹

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Can NAFLD Be Treated or Prevented?

Conventional medicine does not yet have one specific pharmacological treatment that truly works to control NAFLD. People who are at high risk of developing NAFLD, particularly those who are obese or have diabetes or metabolic syndrome conditions, may want to consider talking to their doctor about taking the soybean extract polyenylphosphatidylcholine (PPC). Research suggests that the supplement may stop liver damage in its tracks and even accelerate its regression.²⁶

Phosphatidylcholine (the main component of lecithin) is an integral part of cell membranes, essential for their structural and functional integrity. Cell membranes act like gatekeepers, allowing nutrients into the cells but blocking damaging toxins from gaining entrance. PPC has been shown to enhance cell membrane function throughout the body.

The History of NAFLD

The spectrum of NAFLD came to light as an ailment separate from alcohol-induced fatty liver disease just over 30 years ago. The condition was not named until 10 years later, when in 1980 Dr. J. Ludwig and colleagues at the Mayo Clinic noticed that certain people who shared some common conditions (obesity, diabetes, and elevated cholesterol) had a liver disease that bore a remarkable resemblance to alcoholic liver disease, though none of the individuals drank alcohol. Hence, Dr. Ludwig coined the term nonalcoholic steatohepatitis.³ It took another decade for doctors to finally realize that nonalcoholic steatohepatitis is not a harmless condition, but rather a dangerous one. Since then, scientists, hepatologists (liver specialists), endocrinologists (hormone specialists), and nutritionists have joined forces, scrambling to learn more about the disease that is now known as NAFLD (nonalcoholic fatty liver disease).

PPC already is approved for the treatment of chronic liver diseases in many European countries and is being investigated for treatment of hepatitis (see sidebar on p. 55, “PPC in Viral Hepatitis”). PPC is listed in the Physician’s Desk Reference (PDR) commonly used by US physicians. An accumulating body of research suggests that PPC’s umbrella of protection may extend from the liver to the stomach, pancreas, and cardiovascular system. PPC is well absorbed in humans and animals when taken orally and has no known contraindications, side effects, or interactions with other drugs, even when consumed in large quantities. In one pilot study, researchers found that daily doses of PPC halted the progression of liver fibrosis,²⁷ and a Czech study showed that taking the supplement every day (along with low doses of fatty acids, B vitamins, and vitamin E) reduced fatty-liver symptoms within six months in more than half of the study participants.²⁸ PPC also appears to increase the breakdown of collagen, the connective-tissue protein that tends to accumulate in liver disease, promoting the scarring behind fibrosis and cirrhosis.²⁹

PPC’s protective effect is believed to be the result of its ability to be incorporated in normal and damaged cell membranes. Animal studies have indicated that PPC, which is a polyunsaturated phosphatidylcholine, becomes incorporated in the membranes of liver cells as a substitute for native saturated phosphatidylcholine molecules.³⁰ This substitution is shown to result in an increase in membrane fluidity and active transport activity across the membrane. Similarly, PPC is incorporated in blood lipoproteins such as cholesterol, leading to lipid-lowering properties. In one Russian clinical trial, the supplement lowered total and LDL (“bad”) cholesterol by about 15%, decreased triglyceride levels by 32%, and raised levels of “good” HDL cholesterol by 10%.³¹

PPC also appears to have antioxidant properties, which means it may effectively reduce the oxidative stress (cellular changes that generate cell-damaging free radicals) shown to be a contributing factor in the inflammation and scarring of nonalcoholic steatohepatitis.³²

Experts point out that simply losing weight often will result in a significant reduction of excess fat in the liver. But they add that it is best to lose weight slowly—at a rate of no more than 1 to 2 pounds a week—because rapid weight loss has been shown to exacerbate a fatty liver condition, causing inflammation and even resulting in liver failure.³³

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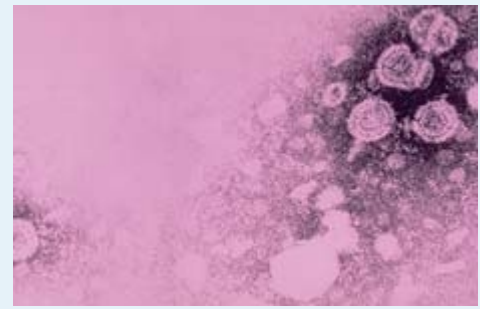
Keeping high glucose levels under control also is critical for NAFLD patients, as research has shown that a fatty liver improves as glucose levels are controlled.³⁶ A preliminary study

found that a drug called metformin (Glucophage®), which improves insulin sensitivity and is used to treat type II diabetes, also significantly lowered liver enzyme levels and decreased fatty deposits in the liver in people with NAFLD.⁷ Additional studies are now under way.

Doctors say that NAFLD can probably be largely prevented and even eliminated in the future by encouraging the adoption of healthy eating habits and more-active lifestyles. For those who already have nonalcoholic fatty liver disease, encouraging discoveries show that the use of natural products may potentially alter the course of this serious consequence of aging and unhealthful lifestyles.

PPC in Viral Hepatitis

PPC (polyenylphosphatidylcholine) has been found to decrease serum aminotransferases in experimental hepatitis. In 1998, Niederau and colleagues conducted a multicenter, randomized, placebo-controlled clinical study evaluating the effects of polyenylphosphatidylcholine (PPC) in combination with interferon alpha (IFN) in patients suffering from hepatitis B and hepatitis C. Although IFN is the standard treatment for these diseases, only 50% of patients with hepatitis B and 20-30% of patients with hepatitis C respond to this antiviral drug with long-term normalization of serum aminotransferases. Of patients with hepatitis C who do respond to IFN while under treatment, at least 50% relapse, which indicates a need for more-effective treatment.



Electron micrograph of hepatitis B virus particles. Hepatitis B causes an inflammation of the liver.

In this study, all 176 patients were given the same amount of interferon during the 24-week test period. In addition, patients were randomly assigned to receive either 1.8 grams per day of PPC or placebo for those 24 weeks. A biochemical response to therapy was defined as a minimum 50% reduction of alanine aminotransferase (ALT) compared to pretreatment values.

The results show that PPC increased the response rate to IFN in chronic viral hepatitis C (71% versus 51% in the placebo group). Prolonged PPC therapy given to responders 24 weeks beyond the cessation of interferon therapy tended to increase the rate of sustained responses in patients with hepatitis C (41% vs. 15%). Hepatitis B patients, however, did not have an improved biochemical response to interferon from PPC.

PPC's beneficial effect in hepatitis C has been the subject of further investigation. Very recently, it was determined that steatosis (fatty liver) is present in a high percentage of patients with chronic hepatitis C. Furthermore, studies have now shown that steatosis is a predictive factor in patients with chronic hepatitis C regardless of viral genotype or body mass index. The studies concluded that hepatic steatosis—whether mild, moderate or severe—appears to be an independent predictor of poor response to therapy.³⁷⁻³⁹

The PPC-interferon study suggests that PPC can be a valuable adjunct to IFN treatment of hepatitis C, and can also be of benefit after cessation of IFN therapy to increase the chance of sustained response to therapy.

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The Liver's Role

The largest organ in the body, the liver has its work cut out for it—performing a wide range of tasks, including processing fats, sugars, proteins, and vitamins, and regulating blood clotting. This vital organ also plays a major role in the body's defense system, filtering and removing toxins and invading microbes from the blood.⁴⁰

The Syndrome X Connection

Because abdominal obesity, insulin resistance, and elevated triglyceride levels all appear to be strongly linked to NAFLD, some researchers advocate classifying NAFLD as an additional feature of the cluster of abnormalities called metabolic syndrome (or Syndrome X).⁴¹ Syndrome X is characterized by the National Institutes of Health as having at least three of the following health concerns: abdominal obesity; high triglyceride levels (150 mg/dL or higher); low

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HDL ("good") cholesterol levels (less than 50 for women and less than 40 for men); moderately elevated or high blood pressure (130/85 or higher); and moderately elevated or high blood sugar levels (a fasting glucose of 110 or higher).

According to the American Medical Association, one in five American adults, or about 47 million, are afflicted with the syndrome, which can more than double one's risk of heart attack, stroke, and diabetes. One study of people with NAFLD found that 88% of those with nonalcoholic steatohepatitis had metabolic syndrome, compared to 55% of patients with simple fatty liver. The researchers concluded that the presence of the syndrome increased the risk of a person with benign fatty liver disease progressing to nonalcoholic steatohepatitis.⁴²

No cure and no single specific treatment are available for metabolic syndrome; today doctors can only treat the various conditions—such as obesity, hypertension, high cholesterol, and diabetes—that are components of the disease.

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