

## THE FIGHT AGAINST FATTY LIVER DISEASE

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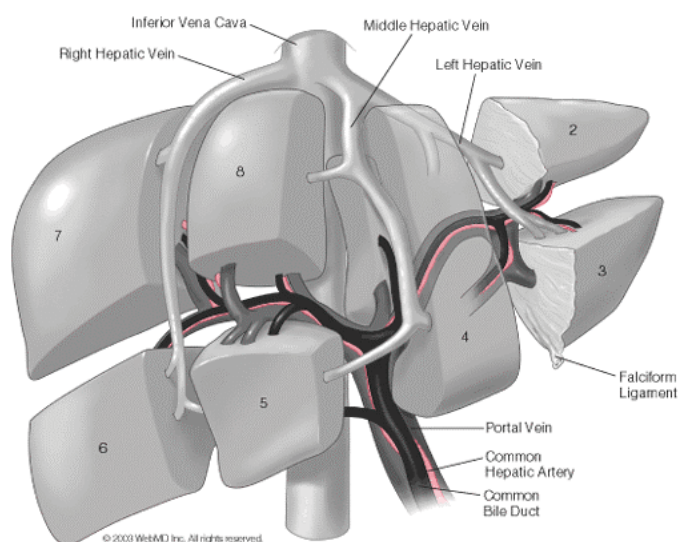
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As the body's largest internal organ, the liver has many critical metabolic functions that become impaired in liver disease. In the United States, fatty liver disease is the most common cause of abnormal liver function tests, and it affects 25-35% of the general population.<sup>1</sup> The most common risk factors for fatty liver disease include excess alcohol, insulin resistance, type 2 diabetes, elevated triglyceride levels and obesity. Fatty liver disease unrelated to alcohol is called non-alcoholic fatty liver disease (NAFLD). Although it's generally considered benign, fatty liver disease can progress to hepatitis and advanced liver disease. The good news is that fatty liver disease can be reversed, and its progression can be halted with dietary and lifestyle changes.

### THE LIVER

The liver is a wedge-shaped organ with an average weight of 3-4 pounds situated in close proximity to the other organs that it regularly communicates with, including the heart and lungs. The prefix hepa refers to the liver. Liver diseases are called hepatic diseases, and doctors who specialize in liver disease are called hepatologists.

Normally a dark reddish-brown, the liver is divided into four major lobes and further divided into segments, lobules, and zones (Figure 1). Different sections of the liver vary in their susceptibility to injury. In most instances of fatty liver disease, cells in the central zone (zone 3) show maximal fat accumulations in liver biopsies. However, in NAFLD caused by protein malnutrition, Kwashiorkor disease (condition of protein malnutrition in children), total parenteral nutrition, phosphorous poisoning, and methotrexate toxicity, maximal fat distribution is found in zone 1.



**FIGURE 1.** Anterior view of the liver. The liver is divided into four major lobes which are further divided into segments. The caudate lobe comprises the posterior segment (not shown). The left lobe comprises the lateral (2), anterior lateral (3), and left medial (4) segments. The right lobe comprises the anterior medial (5), right anterior lateral (6), posterior lateral (7), and posterior medial (8) segments. Image courtesy of WebMD.

### LIVER REGENERATION

Unique among the body's organs, the liver has the ability to regenerate or form new cells as needed. Up to 80% of the liver's cells can be surgically removed or damaged by disease before the liver ceases to function.<sup>2</sup> However, the liver's ability to repair itself and recover from injury varies among individuals. This variability may strongly influence the rate of liver disease severity and progression.

### LIVER CELLS

The liver is primarily made up of liver cells called hepatocytes. The liver also contains immune system cells called Kupffer cells. Kupffer cells can secrete interleukins, tumor necrosis factor, prostaglandins and other chemical cytokines involved in the immune response. Hepatocyte components known as mitochondria are responsible for energy production and fatty acid oxidation.

## THE LIVER'S MANY FUNCTIONS

The liver's cells perform its metabolic functions, helping the body maintain homeostasis. In homeostasis, all of the body's organs and systems work together to maintain health. When liver cells are damaged, they cannot carry out their necessary functions, and this careful orchestration of metabolic events goes awry.

For instance, hepatocytes absorb nutrients from food transported from the intestines, and they separate these nutrients into carbohydrate, fat, and protein molecules. Hepatocytes use these molecules to form hormones, cholesterol, lipids, and proteins, including blood-clotting factors. If the liver cells are unable to produce blood-clotting factors, the blood cannot clot properly, and minor cuts may cause uncontrolled bleeding.

### *Regulation of Minerals and Glucose*

Some proteins synthesized by the liver, called binding or transport proteins, bind with other molecules and transport them throughout the body. Binding proteins, such as albumin, influence the blood concentrations of calcium, magnesium, iron, copper, and most hormones. When the liver can't produce adequate binding proteins, blood levels of these substances fall. Liver cells also respond to stimuli from hormones and nerves to help regulate blood glucose levels. During short periods of fasting the liver breaks down glycogen to provide glucose. During longer periods of fasting the liver produces glucose from amino acids derived from muscle proteins in a process called gluconeogenesis.

### DETOXIFICATION

The body's entire blood supply passes through the liver three times each day. The liver filters and processes this blood and recycles it to the heart and lungs where it is re-oxygenated. In a process called biotransformation, the liver also detoxifies drugs and toxins by converting them from lipophilic (fat soluble) to hydrophilic (aqueous) substances (metabolites) that can be excreted. Certain lipophilic substances such as synthetic dye cannot be metabolized and are excreted intact into bile. For this reason, dye excretion tests, such as the indocyanine green clearance tests, are occasionally used to test the liver's detoxifying abilities. The liver also breaks down thyroid, steroid, and other hormones and helps regulate their levels in the blood.

### LIPID AND LIPOPROTEIN SYNTHESIS

The liver plays a key role in the metabolism of lipids and lipoproteins. Each day, approximately one third of the fatty acids originating from adipose tissue enter the liver. Here, fatty acids are either oxidized or they undergo a process called esterification where they're converted into triglycerides. Oxidation occurs during fasting, and esterification occurs in the non-fasting state. Excessive esterification contributes to fatty liver disease because the excess triglycerides are deposited in vacuoles (holes within

liver cells usually filled with glycogen and lipid). Excess triglycerides widen the vacuoles and displace the other normal cellular components, interfering with normal cell functioning.

Most of the body's cholesterol is produced in the liver. This newly synthesized cholesterol, along with cholesterol of dietary origin, accounts for the liver's stored cholesterol. Daily, hepatocytes produce about twice the amount of cholesterol than they typically take in through diet. Hepatocytes also produce fatty acids through a pathway that involves two enzymes, acetyl-CoA carboxylase and fatty acid synthase. Liver cells also take up fatty acids from the blood, which are derived from diet and from adipose tissue.

Liver cells use cholesterol to synthesize bile acids and to produce liver cell membranes. By utilizing cholesterol, the liver regulates blood cholesterol levels. The liver also uses the bile acids it produces from cholesterol to synthesize bile, a yellow-orange digestive fluid. With the assistance of bile, the liver metabolizes and excretes toxins, medications and alcohol. Surplus bile is collected into the bile duct and stored in the gallbladder where it aids in digestion.

## WHAT IS FATTY LIVER DISEASE?

Fatty liver disease is a condition in which the liver has fat, largely triglyceride, in excess of 5% of the liver weight. Up to 20% of adults and 5% of children are estimated to have fatty liver disease.<sup>3</sup> Fatty liver is also called steatosis. Steatosis is considered benign although it has the potential to worsen. Fatty liver disease is caused by a failure of normal hepatic fat metabolism. This error in metabolism is due to either a defect within the hepatocyte itself or to the delivery of excess fat, fatty acids, or carbohydrates into the liver cells in amounts exceeding their capacity.

### THE NAFLD SPECTRUM

NAFLD is referred to as a spectrum ranging from isolated fatty liver with no symptoms to a form of hepatitis called non-alcoholic steatohepatitis (NASH).<sup>4</sup> In itself, fatty liver disease is considered benign although it can progress. Individuals with NAFLD also have an increased risk of cardiovascular disease.

### WHO IS AFFECTED BY NAFLD?

NAFLD is currently the most common liver disease in the United States as well as worldwide. NAFLD affects an estimated 10-39% of the world's population, and in the US upwards of 30 million Americans have NAFLD, while 8.6 million of these persons have NASH.<sup>5</sup> NAFLD occurs in all age groups and it affects all races. NAFLD is reported to occur in 57-74% of obese individuals, and 90% of morbidly obese individuals.<sup>5</sup> Obesity and the cluster of symptoms known as metabolic syndrome (discussed later in this article) are linked to NAFLD. Yet some people with these risk factors develop the disease

while others do not. A person's ancestry makes some people more prone to liver fat than others. In the United States, NAFLD is more common among Caucasians and Hispanics than among African Americans. As a result of genetic influences, in certain Asian groups NAFLD occurs at a higher rate than expected even in Asian individuals who are not overweight and who do not have other common risk factors.

## NAFLD IN CHILDREN

NAFLD is the most common cause of liver disease in children and its primary cause is obesity. In children, NAFLD causes a particular pattern of liver damage that is most severe in children who are non-white, boys, or are especially obese.<sup>6</sup> In addition, children with NAFLD may be at increased risk for cardiovascular disease.<sup>7</sup> A long-term retrospective study conducted by researchers at Mayo Clinic showed that children with NAFLD are more than 13 times as likely to die over a 20-year period or require a liver transplant as kids in the general population.<sup>8</sup>

### SYMPTOMS AND QUALITY OF LIFE IN CHILDHOOD NAFLD

Researchers have long suspected that childhood NAFLD could cause a diminished quality of life (QOL). To investigate this premise and to evaluate symptoms in pediatric NAFLD, researchers from the University of California, San Diego examined data from 239 children 5-17 years old included in the database of the Nonalcoholic Steatohepatitis Clinical Research Network (CRN). Subjects were from multiple centers within the US. Consistent with pediatric NAFLD, there were more boys than girls in the study.

Half of the subjects reported having 5 or more symptoms. Irritability was the most common individual symptom reported (reported in 73% of children) followed by fatigue, headache, trouble concentrating, and muscle aches or cramps. Irritability was also reported as the most severe symptom, followed by trouble concentrating and fatigue. The three symptoms having the strongest association with QOL were fatigue, trouble sleeping and sadness. The mean total QOL score for children with NAFLD was  $72.7 \pm 15.5$  compared to a score of 83.8 in healthy children. Boys reported significantly higher QOL scores than girls. Overall, nearly 40% of children with NAFLD had impaired QOL scores.<sup>9</sup>

## NASH AND ALCOHOLIC HEPATITIS

Hepatitis is a condition of liver cell inflammation and damage that can be caused by viruses, bacteria, parasites, toxins, and metabolic disorders. Hepatitis can also occur as a result of fatty liver disease. When NAFLD progresses to hepatitis, the condition is called nonalcoholic steatohepatitis (NASH). The overall prevalence of NASH in developed countries is 3 percent.<sup>10</sup> In people who drink excessively the condition is called alcoholic steatohepatitis or alcoholic hepatitis. In alcoholic hepa-

titis and less often in NASH, liver cells can experience severe scarring (which can lead to fibrosis and cirrhosis), and they can experience cell destruction, which causes a serious condition called steatonecrosis. NASH is estimated to progress to cirrhosis at a rate of approximately 10% over a 20-year period.<sup>11</sup>

NAFLD can only be differentiated from NASH with a liver biopsy. A liver biopsy is also necessary to diagnose alcoholic hepatitis, steatonecrosis, fibrosis and cirrhosis.

## NAFLD AND ALCOHOL-INDUCED FATTY LIVER DISEASE

The average daily use of alcohol defines whether fatty liver disease is regarded as NAFLD or alcoholic fatty liver disease. Excessive use of alcohol is commonly defined as greater than 80 grams per day for men and greater than 20 grams daily for women.<sup>12</sup> Both NAFLD and alcoholic fatty liver disease cause similar tissue changes and similar symptoms. However, the clinical course in alcoholic liver disease is usually more progressive.

## SYMPTOMS IN FATTY LIVER DISEASES

Individuals with most types of fatty liver disease have few symptoms unless the condition progresses or presents suddenly (acute disease). Microvesicular fatty liver disease is usually acute and has more serious symptoms.

### SYMPTOMS IN NAFLD AND ALCOHOLIC STEATOSIS

Individuals with steatosis generally remain symptom-free although they may complain of a few symptoms, including:

- Right upper quadrant heaviness and discomfort, which worsens with movement
- Pain felt over the liver, which is usually related to a rapid accumulation of fat associated with alcoholism or diabetes
- Fatigue
- Weight loss
- Liver enlargement (hepatomegaly)
- Acanthosis nigricans, a condition of hyperpigmentation most commonly seen over the neck and under the arm that is seen more often in children

### SYMPTOMS OF NASH AND ADVANCED LIVER DISEASE

Individuals with conditions of NASH and cirrhosis may have the following symptoms:

- Abdominal pain and tenderness
- Dry mouth
- Excessive thirst

- Fatigue
- Fever
- Fluid accumulations in the abdomen (ascites)
- Jaundice (yellowing of skin and eyes)
- Loss of appetite
- Mental confusion
- Nausea
- Unintentional weight gain due to the liver's inability to metabolize fat properly

### SYMPTOMS IN MICROVESICULAR FATTY LIVER DISEASE

Potentially serious symptoms occur in conditions of microvesicular fatty liver disease. These conditions, which include acute fatty liver disease of pregnancy and toxic drug reactions, are associated with steatosis seen only microscopically in liver biopsy specimens. Microvesicular steatosis occurs in 10% of all conditions of NAFLD.<sup>13</sup> Although microvesicular conditions once had a high mortality rate, today, with early diagnosis and treatment, the prognosis has significantly improved. Conditions associated with microvesicular fatty liver disease are listed in the section describing the causes of NAFLD and NASH.

Symptoms of microvesicular fatty liver disease can include:

- Vomiting
- Variable jaundice
- Coma
- Disseminated intravascular coagulation (DIC, a condition of uncontrolled bleeding due to diminished coagulation factors)
- Renal failure
- Raised blood ammonia values
- Hypoglycemia
- Rise in serum fatty acids

In microvesicular fatty liver disease, increased triglyceride accumulations can also be found in the kidneys, heart, brain and pancreas.<sup>14</sup>

### RISK FACTORS FOR FATTY LIVER DISEASE

Nearly all NAFLD occurs as a result of insulin resistance. Besides insulin resistance, risk factors include: obesity, type 2 diabetes, metabolic syndrome, rapid weight loss, malnutrition, high cholesterol levels, high triglyceride levels, gastric bypass surgery, toxins and chemicals,

Wilson's disease (disorder of copper metabolism), certain medications, and genetic factors.

Not surprisingly, NAFLD is observed primarily in developed countries, where a sedentary lifestyle and a high calorie, sugar, and fat intake contribute to obesity, insulin resistance and diabetes. In the US, insulin resistance and obesity are reaching epidemic levels. Reasons for these increases are reported to include increased consumption of high-fructose corn syrup (HFCS), processed carbohydrates, and saturated fatty acids along with decreased consumption of milk and monosaturated and polysaturated fatty acids.

### INSULIN RESISTANCE AND TYPE 2 DIABETES

Insulin normally works to maintain normal blood glucose levels. In insulin resistance, the normal signaling pathways that convey messages between insulin and its target cells become disrupted. Consequently, more insulin is needed for the cells to respond properly, and the pancreas has to produce more insulin. Before insulin resistance develops, affected individuals begin to show signs of overweight and obesity. Eventually, even excess insulin fails to keep glucose levels from rising, and blood levels of glucose and sometimes insulin rise. Genetic factors, pro-inflammatory cytokines including tumor necrosis factor-alpha (TNF- $\alpha$ ), excess weight, and inadequate exercise increase the risk for insulin resistance. Insulin resistance can also be caused by a congenital genetic abnormality that affects insulin receptors. Most insulin resistance occurs as a result of acquired obesity.

Insulin resistance increases the risk for type 2 diabetes and heart disease, and it is the leading cause of NAFLD. About 45% of people in the general population have insulin resistance.<sup>11</sup> Type 2 diabetes develops when insulin resistance leads to persistent elevations of blood glucose. Approximately 70% of people with diabetes have some form of NAFLD and approximately 5-20% of people with diabetes have cirrhosis due to NASH.<sup>12</sup>

Evidence suggests that insulin resistance develops before liver fat becomes excessive. Insulin normally blocks the metabolism of fat molecules in adipose tissue. In insulin resistance, fat cells can't fully respond to insulin. Consequently, the cells convert fat molecules into glycerol and fatty acids, causing elevated blood levels of these substances. Glycerol and fatty acids eventually travel to the liver where they interfere with fat metabolism, causing an accumulation of triglycerides within liver cells.

### OBESITY

Throughout the world, obesity remains a major health problem. In the United States, approximately 300,000 deaths occur each year as a result of obesity.<sup>4</sup> Obesity is a condition of excess body fat. It's estimated that about two-thirds of obese adults and half of obese children may have NAFLD, and about 2-5% of obese adults and 20% of obese children may have NASH.<sup>3</sup>

The normal amount of body fat (expressed as a percentage of body weight) is 25-30% in women, and 18-23% in men. Women with more than 30% body fat and men with more than 25% body fat are considered obese. However, most studies on obesity are based on the BMI. While most people with NAFLD are overweight or obese, not all people with NAFLD are obese. Obesity may increase the risk for developing NAFLD in people exposed to other liver toxins such as alcohol or medications.

### CALCULATING THE BMI

Body fat can also be calculated by using the body mass index or BMI. The BMI is a mathematical formula that takes both weight and height into account. The BMI is calculated as weight in kilograms divided by the square of height in meters. A table with BMI scores provided by Medicinenet.com based on height and weight for adults can be found online at <http://www.medicinenet.com/script/main/art.asp?articlekey=18260>. A BMI table for children and teens can be found at <http://www.medicinenet.com/script/main/art.asp?articlekey=41284>.

In adults, a normal BMI ranges between 20-25 BMI units; overweight as 25-30 BMI units; obesity as 30-35 BMI units; significant obesity as 35-40 BMI units; morbid obesity as 40-45 BMI units; super obesity as 45-50 BMI units; and super-morbid obesity as greater than 50 BMI units. Eighty percent of the deaths related to obesity occur in obese individuals with a BMI greater than 30.<sup>4</sup> In people with fatty liver disease, the BMI correlates with the degree of liver damage, with the greater the BMI score, the greater the extent of liver damage.

Individuals who are morbidly obese will almost inevitably develop significant chronic diseases. Compared to normal weight individuals, those with a BMI  $\geq$  40 are reported as 7.37 times more likely to develop type 2 diabetes.<sup>15</sup> In fatty liver disease, the degree of steatosis parallels the increase in body weight.

### ELEVATED LIPID LEVELS

Elevated blood triglyceride levels are frequently found in individuals with NAFLD. According to the hepatologist Melissa Palmer, individuals with triglyceride levels greater than 200 mg/dL are three times more likely to have NAFLD than people with normal triglyceride levels. In addition, people with low high-density lipoprotein (HDL) cholesterol levels are twice as likely to have NAFLD as people with normal HDL levels.<sup>12</sup>

### METABOLIC SYNDROME

Metabolic syndrome is a cluster of conditions that increase the risk of developing cardiovascular disease and diabetes. Metabolic syndrome has been referred to by many names including Syndrome X and insulin resistance syndrome. It is characterized by any three of the following conditions:

1. Waist measurement of 40 inches or more for men and 35 inches or more for women
2. Triglyceride levels of 150 mg/dL or higher or taking medication for elevated triglyceride levels
3. HDL cholesterol level below 40 mg/dL for men and below 50 mg/dL for women, or taking medication for low HDL levels
4. Blood pressure levels of 120/80 or higher, or taking medication for hypertension
5. Fasting blood glucose levels of 100 mg/dL or higher, or taking medication for elevated blood glucose levels

### GENETIC CAUSES

In March 2010, researchers from Yale University announced their discovery of gene variants that increase the risk for both fatty liver disease and type 2 diabetes.<sup>16</sup> People who carry the variants of a gene for apolipoprotein C3 (APOC3), which produces an enzyme needed for proper fat metabolism, have a higher incidence of both NAFLD and insulin resistance.

Because lean Asians have an inexplicably increased risk of developing NAFLD, the researchers first looked at APOC3 gene variants in 95 lean Asian men. They found that carriers of the gene variant had 5.5% fat in their livers and were markedly insulin-resistant. Because APOC3 inhibits the enzyme that breaks down fats, excess fats are deposited in the liver. Thirty-eight percent of the men with the gene variants had fatty liver disease. In addition, the Yale researchers conducted a similar study on a mixed ethnic group of 163 men and found a similar incidence of fatty liver disease and insulin resistance in those with the gene variants. Testing for the variant could help in identifying individuals at risk for NAFLD and insulin resistance. For people at risk, even modest reductions in weight can reverse the disease process.<sup>16</sup>

Other gene variants have previously been found that cause increased susceptibility to NAFLD. Researchers at the University of Texas Southwestern Medical Center discovered that people with a variant of the gene PNPLA3 have more fat in their livers and an increased risk for liver inflammation. The researchers also found that Hispanics are more likely to carry this genetic variant than African-Americans and Caucasians. This finding explains the increased prevalence of NAFLD in Hispanics.<sup>17</sup>

### CAUSES OF NAFLD AND NASH

The most common causes of NAFLD and NASH include insulin resistance, obesity, type 2 diabetes, metabolic syndrome, and increased triglyceride levels. These causes are considered risk factors and were described in the previous section. NAFLD and NASH can also occur

as a result of certain medical conditions, exposure to various toxins and the use of certain drugs.

### MISCELLANEOUS MEDICAL CONDITIONS ASSOCIATED WITH NAFLD

- Acetylcoenzyme A deficiency
- Autoimmune hepatitis
- Celiac disease
- Glycogen storage diseases
- Hepatitis B
- Hepatitis C
- Obstructive sleep apnea
- Polycystic Ovarian Syndrome (PCOS)
- Tuberculosis
- Wilson's disease

### CAUSES OF MICROVESICULAR FATTY LIVER DISEASE

In microvesicular fat disease, accumulations of fat are seen microscopically. Causes of microvesicular fatty liver disease include:

- Acute fatty liver disease of pregnancy
- Reye's syndrome
- Vomiting disease of Jamaica (caused by eating unripe fruit of the ackee tree)
- Sodium valproate (Depakote) toxicity
- Tetracycline toxicity, seen with intravenous use in obstetrical patients
- Salicylate toxicity
- Congenital defects of urea cycle enzymes
- Genetic mitochondrial fatty acid metabolism defects
- Wolman's disease (rare autosomal recessive lipid storage disease)
- Cholesterol ester storage disease
- Alcoholic foamy fat syndrome
- Delta virus hepatitis, primarily seen in northern South America
- Cocaine toxicity

### ACUTE FATTY LIVER DISEASE OF PREGNANCY

Acute fatty liver of pregnancy is a rare condition of microvesicular fatty liver disease that occurs between the 30th and 38th week of pregnancy. Early symptoms

include nausea and persistent vomiting. Within a week, jaundice usually develops and can be followed by signs of acute liver disease, hypoglycemia, and kidney disease. Severe bleeding may occur although DIC is only seen in about 10% of patients. Miscarriage and early delivery can also occur. Occasionally, fatty liver disease is preceded by hypertension, peripheral edema, and elevated urine protein. An inherited defect in an enzyme involved in fatty acid metabolism is thought to be the cause. Although fatty liver disease used to have a high mortality, with early diagnosis and treatment fetal and maternal mortality is less than 20 percent.<sup>18</sup>

### REYE'S SYNDROME

Reye's syndrome, which usually affects children, was first described in 1963. Through the mid-1970s it was often fatal. With earlier diagnosis, and improved treatments, Reye's disease is now rarely fatal. Reye's syndrome is caused by a generalized mitochondrial dysfunction due to either a virus or toxin or the synergistic effects of these two elements. Aspirin is suspected of triggering Reye's syndrome, which is why it is no longer recommended for children with signs of viral infection.

Reye's syndrome typically occurs within one week of a viral illness usually caused by either influenza B or Varicella and begins with a sudden onset of protracted vomiting, followed by liver enlargement and a rise in liver enzyme levels. It can also cause neurological changes, such as lethargy and confusion, which may deteriorate rapidly into stupor and coma.

### DRUG-INDUCED NAFLD

A number of different drugs and vitamins are known to cause NAFLD in certain individuals. NAFLD usually develops after patients have used the offending drug for 6 months or longer. The reasons for NAFLD development are unclear. Likely, different medications have different effects on fat metabolism, triglyceride production, and insulin regulation. Alcohol used with these medications increases the risk of developing NAFLD. The following drugs have been found to cause NAFLD:

- Amiodarone
- Anti-retroviral drugs used in HIV infection
- Cortisone
- Estrogen derivatives
- Methotrexate
- Perhexiline
- Prednisone
- Sodium valproate
- Tamoxifen
- Tetracycline
- Vitamin A, acute toxicity or chronic use

## OCCUPATIONAL AND OTHER EXPOSURES TO TOXINS

Certain toxic chemicals, especially organic solvents used in dry cleaning, paints, pesticides, and in manufacturing, can induce NAFLD. Information regarding specific chemicals can be found at the Agency for Toxic Substances & Disease Registry <http://www.atsdr.cdc.gov/csem/csem.html>. Chemicals known to cause NAFLD include:

- Benzene
- Carbon tetrachloride
- Chloroform
- Dimethylformamide
- Ethanol
- Hexane
- Methanol
- Phosphorus
- Toluene
- Trichloroethylene (TCE)
- Vinyl chloride

## NUTRIENT DEFICIENCIES ASSOCIATED WITH NAFLD

NAFLD is associated with the following conditions:

- Parenteral nutrition
- Hyperalimentation therapy
- Kwashiorkor disease
- Rapid weight loss
- Protein malnutrition

## GASTRIC BYPASS SURGERY

In older gastric bypass procedures, including the jejunio-ileal intestinal bypass, NAFLD was a significant side effect. Since 2002, the types of gastric bypass surgery commonly used can still cause NAFLD although significantly less often.

## CRYPTOGENIC NAFLD

Conditions of NAFLD with no apparent cause are called cryptogenic. Because cryptogenic NAFLD typically has a delayed diagnosis, it's more likely to progress and is the most common cause of cryptogenic cirrhosis.

## DISEASE PROGRESSION AND REVERSAL IN NAFLD

Factors suspected of causing NAFLD to progress to NASH include:

- Oxidative stress
- Production and release of immune system chemicals known as cytokines, such as TNF- $\alpha$  and leptin, by immune system cells, fat cells, or liver cells

- Liver cell death caused by necrosis or accelerated programmed cell death (i.e., apoptosis)
- Consumption of high-fructose corn syrup has been shown to increase fibrosis in people with NAFLD. In a recent study from Duke University, which included both beverages and foods sweetened with corn syrup, people who regularly consumed corn syrup had more evidence of liver scarring.<sup>19</sup>
- Leptin resistance<sup>10</sup> (a condition in which individuals are resistant to the appetite-curbing effect normally caused by the hormone leptin).

About one-fourth of people with NASH may develop liver scarring (fibrosis) that worsens over time. In some cases significant weight loss has been shown to reverse fibrosis. However, fibrosis that progresses to cirrhosis cannot be reversed. In the US, NASH is an increasingly common reason for liver transplant.

Many people with NASH reverse their conditions (demonstrated by a return to normal liver function tests) with the diet and lifestyle changes described in the Treatment section.

## CRYPTOGENIC CIRRHOSIS

Cryptogenic cirrhosis has no apparent cause. NAFLD is now recognized as the most common cause of cryptogenic cirrhosis.

## ALCOHOLIC LIVER DISEASE

Alcoholism is the most common cause of fatty liver disease. When the liver must process more alcohol than it can handle, its normal ability to break down protein, fats and carbohydrates becomes impaired. Most alcoholic liver disease occurs after many years of excessive drinking. However, not all heavy drinkers develop alcoholic liver disease. Factors that increase risk include genetics, personal susceptibility (viral or autoimmune hepatitis, drug use) and the liver toxicity of different types of alcohol. Women may be more susceptible to alcoholic liver disease than men. Conditions of acute alcoholic hepatitis can result from binge drinking. If severe, acute alcoholic hepatitis can be life threatening.

## SYMPTOMS IN ALCOHOLIC LIVER DISEASE

In alcoholic fatty liver disease, the symptoms are the same as those in NAFLD and NASH. However, patients with alcoholic liver disease can also develop other symptoms related to alcohol toxicity. These include: agitation, bloody stools, cognitive changes, enlarged breasts in males, mood changes, and vomiting blood.

## DISEASE PROGRESSION IN ALCOHOLIC LIVER DISEASE

- \* Fatty liver is the first stage. It occurs in nearly everyone who drinks heavily and improves with alcohol abstinence.

- \* Alcoholic hepatitis occurs in up to 35% of heavy drinkers.<sup>20</sup> In its mild form alcohol hepatitis can remain stable for years before causing progressive liver damage. Liver damage can be reversed with alcohol abstinence. In its severe form, which can occur after binge drinking, it can quickly progress and cause life-threatening complications.
- \* Alcoholic cirrhosis is the most serious stage. In cirrhosis, normal liver tissue is replaced with scar tissue (fibrosis). According to the American Liver Foundation, between 10% and 20% of heavy drinkers develop cirrhosis, usually after 10 or more years of drinking. Cirrhosis is not reversible although the condition can stabilize and stop progressing with alcohol abstinence.<sup>20</sup>

## DIAGNOSING FATTY LIVER DISEASE

In the early stages, before any symptoms occur, fatty liver disease is often first suspected when blood tests for liver enzymes are elevated. Fatty liver may also be suspected when it presents as a diffuse, smooth, enlarged liver in conditions of obesity, diabetes, or alcoholism. In some instances, the first hint of fatty liver occurs when fat deposits are seen on ultrasound or other imaging tests.

### LABORATORY LIVER FUNCTION TESTS

Blood liver function tests, despite their name, do not directly measure the liver's function. Rather, these tests indirectly measure the liver's integrity and the ability of the biliary system (liver, bile ducts, gallbladder) to do its job.

#### ENZYME LEVELS

Liver cells contain a number of metabolic enzymes. In liver disease, serum enzyme levels rise as enzymes are released from damaged liver cells. Specific enzyme elevations vary in different diseases. The enzymes primarily used to help diagnose fatty liver disease include: 1) alanine aminotransferase (ALT), which is also called serum glutamic pyruvate transaminase or SGPT and 2) aspartate aminotransferase (AST), which is also called serum glutamic-oxalocetic transaminase or SGOT. ALT and AST are usually but not always elevated in fatty liver disease.

Besides the liver, ALT and AST are present in other organs, particularly the heart, skeletal muscle, and pancreas. Therefore, elevated AST and ALT levels are seen in other diseases and are not specifically caused by liver disease. In the US, NAFLD is the most common cause of mildly elevated liver enzymes in asymptomatic individuals.

Elevations of AST and ALT in NAFLD are usually modest and not higher than four times the upper limit of the reference range, which is usually 40-45 IU/L. The degree of enzyme elevation does not necessarily correlate with the degree of fat accumulation or inflammation. In NAFLD, the ALT usually shows more of an elevation than the AST level. In alcoholic liver disease, the AST is usually higher than the ALT level.

### BILIARY FUNCTION TESTS

The biliary-excretory function of the liver and gallbladder can be assessed indirectly with laboratory tests for bilirubin, and the enzymes alkaline phosphatase (ALP or AP), and gamma-glutamyl transferase (GGT). Elevations of bilirubin, a yellow pigment that causes jaundice, occur in liver disease and in any condition involving the breakdown of red blood cells. The enzyme ALP is present in both the liver and the bone. If the ALP level is elevated, the GGT test can help determine if the elevation is from liver or bone disease. GGT is a sensitive although non-specific indicator of liver disease. Elevations of both ALP and GGT suggest biliary disease.

### PROTEINS AND CLOTTING FACTORS

Because the liver synthesizes most of the body's proteins, including clotting factors, blood-clotting tests can also be used to indirectly evaluate liver function. As liver function fails, levels of the coagulation factors (I, II, V, VII, IX, X, IXX, and XIII) start to fall and levels of prothrombin (PT) rise. Improvements in the PT result indicate a transient loss of hepatic function, whereas a prolonged rise in PT suggests marked liver failure.<sup>2</sup> Blood ammonia elevations are also seen in liver disease, especially advanced liver disease and hepatic encephalopathy. Most abnormal liver function results occur before clinical changes become apparent.

### OTHER LAB TESTS

Many individuals with NAFLD, especially men, have high transferrin and ferritin levels, suggesting iron overload. The incidence of having a genetic disposition for hemochromatosis is higher among people with NAFLD. Insulin levels are frequently elevated in individuals who have both NAFLD and insulin resistance.

### LIVER BIOPSY

Liver biopsy is the best test for diagnosing fatty liver disease, steatohepatitis, the development of fibrosis and cirrhosis. In a liver biopsy, which may be guided by ultrasound or CT imaging techniques, a sample of the liver is removed by inserting a needle into the tissue. The sample is then examined in the laboratory. Excess liver fat may be seen with the naked eye (i.e., macrovesicular fat) or with stained preparations viewed through a microscope (i.e., microvesicular fat).

In fatty liver, accumulations of fat can range as high as 40% of the liver's weight. Although liver fat in itself is benign, the appearance of liver cells showing signs of fat-induced damage, inflammation, or destruction (i.e., steatonecrosis) is serious. Cell death occurs by necrosis or apoptosis (i.e., accelerated programmed cell death). In steatonecrosis, hepatocytes may appear swollen with distorted nuclei, and the cells may show evidence of fibrosis or disease progression to cirrhosis or liver cancer.

Because liver biopsy is an invasive procedure with potential serious side effects, numerous researchers have

attempted to develop scoring systems to diagnose conditions of fatty liver disease on the basis of imaging and laboratory tests. While some methods have advantages over others, none have the diagnostic precision of the liver biopsy.

### NAFLD ACTIVITY SCORE

Changes seen on biopsy determine the staging of disease. Specific findings include:

1. Presence of steatosis (usually macrovesicular although it may be microvesicular or mixed).
2. Signs of inflammation such as mixed neutrophilic and mononuclear white blood cells.
3. Abnormal cellular changes such as ballooning degeneration, distorted nucleus, abnormal granules.
4. Fibrosis.

Steatosis, inflammation, and cellular changes are used to calculate the NAFLD activity score, which is graded from 0-8.

### FIBROSIS

All cellular injury induces fibrosis as an adaptive or healing response, with the duration of injury and genetic factors determining whether fibrosis progresses to cirrhosis and ultimately liver cancer.

### IMAGING TESTS

In fatty liver disease, imaging tests are used to assess the liver's integrity and to identify the presence of excess fat.

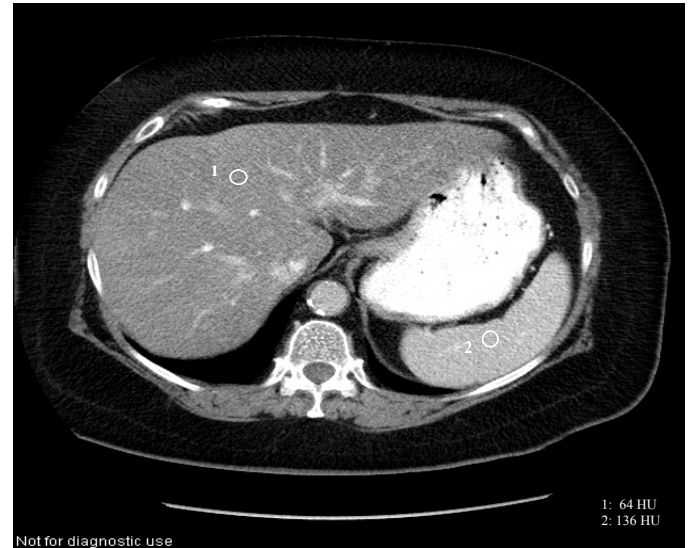
#### ULTRASOUND

In severe cases diffuse fatty liver is usually easy to recognize on ultrasound as the liver appears markedly echogenic and attenuates the ultrasound beam. More subtle cases may be difficult to detect, however. In focal fatty liver, patchy areas of increased echogenicity are seen. Diabetics, alcoholics, the obese, individuals on hyperalimentation therapy, and individuals with Cushing's syndrome have increased risk for focal fatty liver disease. Ultrasound may show a bright echo pattern in fatty liver disease although in some cases of steatosis the ultrasound may be normal.

#### COMPUTED TOMOGRAPHY (CT)

CT scans in fatty liver disease reduce the CT attenuation of the involved liver. With fatty infiltration, the liver is at least 10 HU lower than that of the spleen. Although it is most commonly a diffuse process (hence the lower attenuation is seen throughout the liver), fatty infiltration can also be focal and inhomogenous. In the latter case it can be difficult to differentiate from tumorous mass. Dual energy CT helps to differentiate focal fat from other low-

density lesions. Fatty infiltrate (either diffuse or focal) is most accurately assessed on noncontrast CT. Many operators include a region of interest (ROI) measurement of the liver and of the spleen. A spleen measurement that is more than 10 HU higher than that of the liver indicates fatty infiltrate of the liver (Figure 2).



**FIGURE 2.** A region-of-interest (ROI) measurement is placed within the liver and spleen. If the spleen measures 10 HU or more than the liver, fatty infiltrate of the liver is indicated.

### MAGNETIC RESONANCE IMAGING (MRI)

Magnetic resonance imaging (MRI) may be useful for excluding fatty liver disease. Chemical-shift MRI correlates with the quantitative assessment of fatty infiltration across the entire range of liver disease. T1-weighted gradient-echo opposed-phased images demonstrate loss of signal compared to T1-weighted GRE in-phase image and may help in identifying areas of focal fat.

## TREATMENT OF FATTY LIVER DISEASE

Treatment of fatty liver disease involves treating its major causes including obesity, insulin resistance, type 2 diabetes, and alcoholism. Losing weight is considered the most important factor in treating NAFLD, and abstaining from alcohol is considered the most important factor for alcoholic liver disease. Several different medical treatments are also used, primarily for their ability to reduce risk factors and specific causes. No other established treatments are available for NASH.

### DIET AND LIFESTYLE

Recommendations for reversing NAFLD and NASH include:

- Losing weight safely, no more than 1-2 pounds weekly

- Lowering triglyceride levels through dietary changes or medications
- Avoiding alcohol, unnecessary drugs, and environmental toxins
- Controlling blood sugar levels if insulin resistance or diabetes are present
- Following a balanced healthy diet
- Increasing physical activity
- Having regular check-ups and liver function tests

## DIETS

Weight loss can improve insulin sensitivity, reduce adipose tissue inflammation, and reduce the liver's levels of free fatty acids. It's recommended that weight loss occur slowly, and it must be sustained or steatosis will recur. Rapid weight loss methods may worsen NAFLD and lead to the development of cholelithiasis. A weight loss of 10 percent leads to a significant decrease in liver enzyme levels and in some cases a return to normal levels. While there is no single diet recommended for NAFLD, diets should be low in saturated fats and simple refined carbohydrates and high in fiber.

Increased consumption of dietary fiber is associated with improved lipid levels and weight loss. Consumption of specific nutrients can also facilitate weight loss. Calcium, especially calcium derived from dairy products, is reported to decrease the incidence of insulin resistance syndrome and obesity. Vitamin D is also essential for the proper absorption of calcium. With inadequate vitamin D, only 10-15 percent of dietary calcium is absorbed. In obesity, vitamin D levels are often inadequate because vitamin D is fat soluble and stored in the body's fat deposits that aren't available for use.<sup>15</sup>

Even in non-overweight individuals with NAFLD, diet offer benefits because it reduces weight centered around the midsection. Abdominal (or central) obesity may cause NAFLD, even in individuals of normal weight. Researchers at St. Louis University have found that a weight loss of at least 9 percent can reverse NASH.<sup>21</sup>

## THE IMPORTANCE OF EXERCISE

Exercising for at least 30 minutes, even in several short sessions, most days of the week is reported to help increase metabolism and assist with weight loss. A combination of aerobic and weight-bearing exercises is recommended. Improvement in insulin resistance is reported to correlate with the intensity of an individual's exercise program. Benefits from exercise may be realized even without a significant accompanying weight loss. Exercise increases insulin sensitivity by increasing muscle mass.

## WEIGHT LOSS MEDICATIONS

The three FDA-approved medications approved for weight loss include: phentermine, sibutramine and orlistat. In addition, methamphetamine (Desoxyn) is

approved for the treatment of morbid obesity. These medications have not been well studied for their effects in NAFLD. Because of their effects on nutrient absorption, they aren't generally recommended for treating NAFLD. Clinical trials suggest that orlistat can improve liver function in NAFLD and inflammation in NASH if it's accompanied by weight loss.

## MEDICAL AND SURGICAL THERAPIES

Most drug therapies aim to reduce the various risk factors for NAFLD, with specific therapies prescribed on the basis of the individual's unique metabolic history. Most drugs in use for NAFLD are still under investigation and are also being evaluated for their use in reducing inflammation and steatosis in NASH.

## DRUG THERAPIES

- Lipid-lowering agents and anti-diabetes medications are being evaluated in multiple ongoing national studies.
- Rimonabant
- Ursodeoxycholic acid (UDCA, ursodiol), a naturally-occurring bile acid long used in primary biliary cirrhosis, has shown improvement in NAFLD and NASH. As an antioxidant, UCDA reduces oxidative stress and reduces liver inflammation and appears to reduce liver damage in cases of steatohepatitis. Study results, however, have been conflicting and UCDA is not considered promising as a sole therapeutic agent.

### *Statin Lipid Lowering Agents.*

Overall, statins are known to decrease mortality in patients with diabetes mellitus and cardiovascular disease. In a recent multi-center, double-blind study of 326 subjects with elevated lipid levels and chronic liver disease, high-dose pravastatin showed no significant alterations in liver enzyme levels. This study confirms earlier investigations showing that statins are safe and effective in lowering lipid levels in patients with NAFLD although their role in treating NASH is less clear. In a small pilot study of 4 patients with NASH, an improvement in liver inflammation occurred in 3 patients and improved steatosis occurred in the other patient. In one recent Swedish study, 68 patients with NAFLD began statin treatment and were retested 10-16 years after their baseline biopsies. Although these patients initially had high BMI levels and higher rates of diabetes, after statin treatment they experienced a significant reduction in hepatic steatosis and a lower rate of fibrosis progression compared to untreated patients.<sup>11</sup> Likewise, a 1-year study of atorvastatin showed improvement in tissue studies.<sup>1</sup>

### *Thiazolidineiones (TZDs).*

In small non-controlled trials, thiazolidineiones (glitazones) such as pioglitazone and rosiglitazone, have been shown to decrease inflammation of the liver in humans

and rats during active drug therapy. Insulin sensitivity also improved although there was universal weight gain, primarily fat gain.

In a small study of pioglitazone combined with diet compared to diet alone, pioglitazone showed improvement of liver enzyme levels and steatosis, and an improvement in fibrosis was seen in the first 6 months of treatment. The differences between the pioglitazone and control group was not significantly different. A 48-week study of rosiglitazone in 30 patients showed improvement in laboratory function tests and tissue studies. However, the US Food and Drug Administration issued an alert in 2007 that rosiglitazone potentially caused an increased risk of myocardial infarction and heart-related mortality.<sup>1</sup>

Although several TZD trials have shown improvement in NASH, the FLIRT trial, which followed 63 patients treated for one year with either rosiglitazone or placebo, showed conflicting results. Although the patients using rosiglitazone showed improvements in serum enzyme levels, insulin sensitivity, and liver fat, they did not show improvements in the NAFLD activity score or in overall fibrosis. Side effects of TZDs include universal weight gain that does not always resolve with discontinuation of medicine and lower extremity edema, which is seen in up to 5 percent of patients.<sup>11</sup>

Metformin, a drug therapy for diabetes mellitus, has been shown to improve blood glucose levels by decreasing hepatic glucose production and increasing the utilization of glucose in peripheral skeletal muscles. Clinical trials to date have shown mixed histology results suggesting that metformin is not ideal as a sole therapy for NASH although some improvement in liver function in NAFLD has been seen.

Incretin analogs are a newer class of injectable diabetes medications that act as glucagon-like-protein-1-receptor agonists that are being investigated for their potential benefits in NASH. Incretin analogs increase insulin secretion, slow gastric emptying and increase satiety. They've been shown to cause modest weight loss, although nausea is a common side effect.

Rimonabant is a selective cannabinoid receptor antagonist that decreases lipid production in the liver while increasing satiety, adiponectin levels and glucose uptake, improving both insulin levels and lipid profiles. Originally developed as a weight loss medication, rimonabant is being evaluated for its use in NAFLD and NASH.

### SURGICAL THERAPIES

In some cases of fatty liver disease, bariatric surgery is recommended although it is solely used for obese individuals who are at least 80 to 100 pounds overweight with BMI scores between 35 and 40 BMI units.<sup>12</sup> Bariatric surgery with appropriate weight loss is reported to improve liver function tests and tissue studies in NASH.

Roux-en-Y gastric bypass has shown sustained improvement in biopsies taken 2 years after the procedure in nearly all patients. In numerous studies, Roux-en-

Y, and also the laparoscopic adjustable band procedure, have shown significant improvements in steatosis, hepatocellular injury and fibrosis. In studies, 75-100 percent of patients saw complete reversal of NASH. Using biliopancreatic diversion surgery, improvement was seen in steatosis although some patients experienced improvement in fibrosis and some experienced a worsening of fibrosis.<sup>11</sup> In a small minority of patients any type of bariatric surgery may develop either worsening steatohepatitis or mild fibrosis.

However, in some cases, surgical reversal of intestinal bypass for obesity is required when it leads to rapid weight loss and NAFLD. The early jejunio-ileal intestinal bypass, in particular, causes malabsorption and nutrient loss, causing liver abnormalities in up to 40 percent of patients and severe NASH accompanied by liver failure in 6 percent of patients.<sup>12</sup>

Liver transplants are increasingly being performed for conditions of steatohepatitis with survival rates over 90%.<sup>22</sup> In some cases, transplanted livers may also develop fatty liver disease.

### THERAPIES FOR SPECIFIC MEDICAL CONDITIONS

- \* Individuals with NAFLD associated with celiac disease or gluten sensitivity can reverse fatty liver disease by following a gluten-free diet.
- \* Individuals with growth hormone deficiency who receive growth hormone have been reported to reverse NASH.
- \* Patients with obstructive sleep apnea have increased risk of NAFLD presumably related to elevations of cortisol and TNF- $\alpha$ . Patients who receive adequate treatment show improvement in liver function tests.<sup>23</sup> Further studies are needed to tell if treatment can help delay or prevent the development of NAFLD.

### ALTERNATIVE MEDICINE

Researchers have studied vitamin supplements, particularly antioxidants, to see if they could reduce the effects of inflammation. To date, studies haven't supported the use of vitamins. However, both vitamin E and betaine have shown some encouraging results and further investigation is needed. Overall, antioxidant therapy hasn't been useful because current therapies are unable to penetrate the cell mitochondria and impact the development of reactive oxygen species.

### CONCLUSION

In the United States, the high incidence of fatty liver disease in both adults and children is predominantly related to the modern American diet. Although there are a number of other rare causes, most instances of fatty liver disease that are not caused by alcohol are due to obesity, insulin resistance, type 2 diabetes or elevated blood lipid levels. Although fatty liver disease causes few if any

symptoms, it has the potential to progress to hepatitis, cirrhosis, liver cancer and liver failure. An increasing number of liver transplants are being performed in individuals with complications stemming from fatty liver disease. With dietary changes and weight loss, this disorder may be prevented, even in people at high risk, and its progression to hepatitis may be halted. However, once fibrosis and cirrhosis develop, the liver damage cannot be reversed.

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## FATTY LIVER DISEASE POST TEST

Expires: August 15, 2012 Approved for 2 ARRT Category A Credits.

1. **What is the most common cause of abnormal liver function tests in the United States?**
  - a. Hepatitis C
  - b. Fatty liver disease
  - c. Cirrhosis
  - d. Gallstones
2. **What percentage of liver cells needs to be destroyed before the liver ceases to function?**
  - a. 20%
  - b. 40%
  - c. 80%
  - d. 100%
3. **How many times daily does the body's entire blood supply pass through the liver?**
  - a. 3
  - b. 5
  - c. 8
  - d. 10
4. **What organ produces most of the body's cholesterol?**
  - a. The gallbladder
  - b. The thyroid gland
  - c. The liver
  - d. The pancreas
5. **What percentage of children have fatty liver disease?**
  - a. 5%
  - b. 15%
  - c. 25%
  - d. 30%
6. **What is another name for fatty liver disease?**
  - a. Steatohepatitis
  - b. Steatosis
  - c. Steatonecrosis
  - d. Sclerosing cholangitis
7. **Individuals with NAFLD are at risk of developing**
  - a. cardiovascular disease.
  - b. thyroid disease.
  - c. stroke.
  - d. hemochromatosis.
8. **What percentage of morbidly obese persons develop NASH?**
  - a. 50%
  - b. 70%
  - c. 90%
  - d. 100%
9. **What is the primary cause of NAFLD in children?**
  - a. Diabetes
  - b. Obesity
  - c. Alcohol
  - d. Overuse of antibiotics
10. **Hepatitis is a condition of**
  - a. fatty liver.
  - b. jaundice.
  - c. liver cell damage and inflammation.
  - d. liver malignancy.
11. **How is NAFLD differentiated from NASH?**
  - a. Liver biopsy
  - b. CT scan
  - c. Enzyme levels
  - d. Ultrasonography
12. **What percent of individuals with NAFLD have microvesicular fatty liver disease?**
  - a. 10%
  - b. 30%
  - c. 50%
  - d. 70%
13. **What does nearly all NAFLD occur as a result of?**
  - a. Insulin resistance
  - b. Fast food
  - c. Diabetes
  - d. Alcoholism
14. **What percentage of people in the general population have insulin resistance?**
  - a. 15%
  - b. 45%
  - c. 60%
  - d. 75%
15. **How many deaths occur each year as a result of obesity?**
  - a. 300,000
  - b. 700,000
  - c. 1.5 million
  - d. 3 million
16. **How much more likely is NAFLD in people with triglyceride levels higher than 200 mg/dL, compared to people with normal levels?**
  - a. 3 times
  - b. 6 times
  - c. 8 times
  - d. 10 times
17. **What causes an increased risk of NAFLD in Hispanics and Asians?**
  - a. Diet
  - b. Gene variants
  - c. Vitamins
  - d. Exposure to environmental toxins
18. **When does acute fatty liver of pregnancy usually occur?**
  - a. 4-12 weeks
  - b. 12-20 weeks
  - c. 20-28 weeks
  - d. 30-38 weeks
19. **Conditions of NAFLD with no apparent cause are called**
  - a. Syndrome X.
  - b. cryptogenic.
  - c. NASH.
  - d. abiogenic.
20. **One of the factors suspected of causing NAFLD to progress to NASH is**
  - a. vitamin deficiency.
  - b. leptin resistance.

- c. too much exercise.  
d. excessive exposure to sunlight.
- 21. Acute alcoholic hepatitis can result from**
- binge drinking.
  - drinking for many years.
  - abstaining from alcohol.
  - drinking one glass of red wine each day.
- 22. In NAFLD, the ALT is usually \_\_\_\_\_ the AST level.**
- equal to
  - higher than
  - half of
  - one quarter of
- 23. On CT scan, fatty liver shows up as**
- low density compared with the spleen.
  - high density compared with the spleen.
  - having the same density as the spleen.
  - a central area of low density surrounded by a periphery of high density
- 24. What percentage of weight loss has been found to reverse conditions of NASH?**
- 3%
  - 6%
  - 9%
  - 18%
- 25. What weight loss drug can help with NAFLD and NASH if it's accompanied by weight loss?**
- Orlistat
  - Phentermine
  - Levothyroxine
  - Dexfenfluramine
- 26. What lipid-lowering drugs have shown improvement in NAFLD?**
- Metformin compounds
  - Statins
  - Beta-blockers
  - Calcium channel blockers
- 27. Patients with NAFLD are candidates for bariatric surgery if**
- their liver disease has progressed to NASH.
  - they are also diabetic.
  - are at least 80 lbs overweight.
  - are less than 50 lbs overweight.
- 28. What percentage of patients having Roux-en-Y or the laparoscopic adjustable-band procedure have shown complete reversal of NASH?**
- 0%
  - 10-20%
  - 45-70%
  - 75-100%
- 29. What is the survival rate for patients undergoing liver transplant procedures for steatohepatitis?**
- 20%
  - 50%
  - 75%
  - 90%
- 30. What improves NAFLD in patients that also have celiac disease?**
- Eating small meals more frequently
  - A gluten-free diet
  - Statins
  - Controlling blood glucose levels



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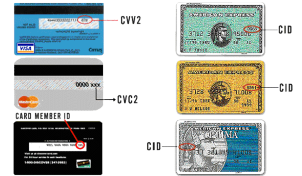
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