Review Article

Medical Progress

Nonalcoholic Fatty Liver Disease

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NONALCOHOLIC fatty liver disease is an increasingly recognized condition that may progress to end-stage liver disease. The pathological picture resembles that of alcohol-induced liver injury, but it occurs in patients who do not abuse alcohol.[1,2] A variety of terms have been used to describe this entity, including fatty-liver hepatitis, nonalcoholic Laënnec's disease, diabetes hepatitis, alcohol-like liver disease, and nonalcoholic steatohepatitis. Nonalcoholic fatty liver disease is becoming the preferred term, and it refers to a wide spectrum of liver damage, ranging from simple steatosis to steatohepatitis, advanced fibrosis, and cirrhosis. Steatohepatitis (nonalcoholic steatohepatitis) represents only a stage within the spectrum of nonalcoholic fatty liver disease. The clinical implications of nonalcoholic fatty liver disease are derived mostly from its common occurrence in the general population and its potential to progress to cirrhosis and liver failure. Nonalcoholic fatty liver disease should be differentiated from steatosis, with or without hepatitis, resulting from secondary causes (Table 1), because these conditions have distinctly different pathogeneses and outcomes.

EPIDEMIOLOGIC FEATURES

Risk Factors

Obesity, type 2 (non-insulin-dependent) diabetes mellitus, and hyperlipidemia are coexisting conditions frequently associated with nonalcoholic fatty liver disease. The reported prevalence of obesity in several series of patients with nonalcoholic fatty liver disease varied between 30 and 100 percent, the prevalence of type 2 diabetes varied between 10 and 75 percent, and the prevalence of hyperlipidemia varied between 20 and 92 percent.[1,3-18] Some children with nonalcoholic fatty liver disease have type 1 diabetes mellitus.[17,18] The prevalence of nonalcoholic fatty liver disease increases by a factor of 4.6 in obese people, defined as those with a body-mass index (the weight in kilograms divided by the square of the height in meters) of at least 30.[19] Regardless of body-mass index, the presence of type 2 diabetes mellitus significantly increases the risk and severity of nonalcoholic fatty liver disease.[20,21] Truncal obesity seems to be an important risk factor for nonalcoholic fatty liver disease, even in patients with a normal body-mass index.[22] About half of patients with hyperlipidemia were found to have nonalcoholic fatty liver disease on ultrasound examination in one study.[23] Hypertriglyceridemia rather than hypercholesterolemia may increase the risk of nonalcoholic fatty liver disease.[23]

A family history of steatohepatitis or cryptogenic cirrhosis has also been implicated as a risk factor for this disorder.[24] Nonalcoholic fatty liver disease may affect persons of any age and has been described in most racial groups. In most series, the typical patient with nonalcoholic fatty liver disease is a middle-aged woman,[1,3-7,11,14] but some have found a higher prevalence of nonalcoholic fatty liver disease in males than in females.[25-28]

Prevalence

Nonalcoholic fatty liver disease affects 10 to 24 percent of the general population in various countries. The prevalence increases to 57.5 percent[25] to 74 percent[19,26] in obese persons. Nonalcoholic fatty liver disease affects 2.6 percent of children[27] and 22.5 percent[27] to 52.8 percent[29] of obese children.

Nonalcoholic fatty liver disease is a common explanation for abnormal liver-test results in blood donors, and it is the cause of asymptomatic elevation of aminotransferase levels in up to 90 percent of cases once other causes of liver disease are excluded.[30] Nonalcoholic fatty liver disease is the most common cause of abnormal liver-test results among adults in the United States.[31]

The prevalence of nonalcoholic fatty liver disease in the United States is unknown, although a good estimate can be made from the known prevalences of obesity and type 2 diabetes mellitus in the general population. Obesity affects 22.5 percent of people 20 years of age or older.[32] Steatosis is found in over two thirds of the obese population, regardless of diabetic status,[20] and in more than 90 percent of morbidly obese persons (those weighing more than 200

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TABLE 1. CAUSES OF FATTY LIVER DISEASE.

NUTRITIONAL	DRUGS*	METABOLIC OR GENETIC	OTHER
Protein-calorie malnutrition†	Glucocorticoids†	Lipodystrophy†	Inflammatory bowel disease†
Starvation†	Synthetic estrogens†	Dysbetalipoproteinemia†	Small-bowel diverticulosis with bacterial overgrowth†
Total parenteral nutrition†	Aspirin‡	Weber–Christian disease†	Human immunodeficiency virus infection†
Rapid weight loss†	Calcium-channel blockers†	Wolman's disease§	Environmental hepatotoxins
Gastrointestinal surgery for obesity†	Amiodarone§	Cholesterol ester storage§	Phosphorus‡
	Tamoxifen†	Acute fatty liver of pregnancy‡	Petrochemicals†‡
	Tetracycline‡		Toxic mushrooms†
	Methotrexate†		Organic solvents
	Perhexiline maleate§		*Bacillus cereus* toxins‡
	Valproic acid‡		
	Cocaine‡		
	Antiviral agents		
	Zidovudine†		
	Didanosine‡		
	Fialuridine‡		

*This is a partial list of agents that produce fatty liver. Some drugs produce inflammation as well. The association of fatty liver with calcium-channel blockers and valproic acid is weak, whereas the association with amiodarone is strong. Drug-induced fatty liver may have no sequelae (e.g., cases caused by glucocorticoids) or can result in cirrhosis (e.g., cases caused by methotrexate and amiodarone).

†This factor predominantly causes macrovesicular steatosis (mostly owing to imbalance in the hepatic synthesis and export of lipids).

‡This factor predominantly causes microvesicular steatosis (mostly owing to defects in mitochondrial function).

§This factor causes hepatic phospholipidosis (mostly owing to the accumulation of phospholipids in lysosomes).

percent of their ideal body weight).[21] Steatohepatitis affects about 3 percent of the lean population (those weighing less than 110 percent of their ideal body weight), 19 percent of the obese population, and almost half of morbidly obese people.[20,21] Hence, on the basis of the U.S. population in the year 2000,[33] an estimated 30.1 million obese adults in this country may have steatosis, and about 8.6 million may have steatohepatitis. Diabetes mellitus affects 7.8 percent of the U.S. adult population,[34] whereas about 50 percent (range, 21 to 78 percent)[35] of patients with diabetes (7.8 million people) have nonalcoholic fatty liver disease.

The association of diabetes and obesity may pose an added risk: among severely obese patients with diabetes, 100 percent were found to have at least mild steatosis, 50 percent had steatohepatitis, and 19 percent had cirrhosis.[36]

The prevalence of nonalcoholic fatty liver disease in the United States seems to be substantially greater than the 1.8 percent prevalence of hepatitis C virus infection.[37] The figures, however, may underestimate the real prevalence of nonalcoholic fatty liver disease, since many patients are nonobese and nondiabetic, and the disease is increasingly diagnosed in children and adolescents.

CLINICAL MANIFESTATIONS

Clinical Features

Most patients with nonalcoholic fatty liver disease have no symptoms or signs of liver disease at the time of diagnosis, although many patients report fatigue or malaise and a sensation of fullness or discomfort on the right side of the upper abdomen. Hepatomegaly is the only physical finding in most patients. Acanthosis nigricans may be found in children with nonalcoholic fatty liver disease.[17,18] Findings of chronic liver disease and diminished numbers of platelets suggest that advanced disease with cirrhosis is present. A high proportion of patients with cryptogenic cirrhosis share many of the clinical and demographic features of patients with nonalcoholic fatty liver disease,[38] suggesting that their cryptogenic cirrhosis is unrecognized nonalcoholic fatty liver disease.

Laboratory Abnormalities

Mildly to moderately elevated serum levels of aspartate aminotransferase, alanine aminotransferase, or both are the most common and often the only laboratory abnormality found in patients with nonalcoholic fatty liver disease. The ratio of aspartate aminotransferase to alanine aminotransferase is usually less than 1, but this ratio increases as fibrosis advances, leading to a loss of its diagnostic accuracy in patients with cirrhotic nonalcoholic fatty liver disease.[14] Serum alkaline phosphatase, γ-glutamyltransferase, or both are above the normal range in many patients, although their degree of elevation is less than that seen in alcoholic hepatitis.[4,5,11] Other abnormalities, including hypoalbuminemia, a prolonged prothrombin time, and hyperbilirubinemia, may be found in patients with cirrhotic-stage nonalcoholic fatty liver

disease. Elevated serum ferritin levels are found in half the patients,[8,14] and increased transferrin saturation is found in 6 to 11 percent of patients.[8,14,16] Hepatic iron index[8,13,14,16] and the hepatic iron level,[13,14,16] however, are usually in the normal range. It has been suggested that heterozygosity for the hemochromatosis (*HFE*) gene may be increased in nonalcoholic fatty liver disease and that hepatic iron overload may be associated with more severe liver disease.[12,39] Clinical data from large numbers of patients, however, have shown that this is not always the case.[13,14,16,40-42]

Imaging Studies

On ultrasonography, fatty infiltration of the liver produces a diffuse increase in echogenicity as compared with that of the kidneys. Regardless of the cause, cirrhosis has a similar appearance on ultrasonography. Ultrasonography has a sensitivity of 89 percent and a specificity of 93 percent in detecting steatosis and a sensitivity and specificity of 77 percent and 89 percent, respectively, in detecting increased fibrosis.[43]

Fatty infiltration of the liver produces a low-density hepatic parenchyma on computed tomographic (CT) scanning. Steatosis is diffuse in most patients with nonalcoholic fatty liver disease, but occasionally, it is focal. Consequently, ultrasonography and CT scans may be misinterpreted as showing malignant liver masses.[44] In such cases, magnetic resonance imaging can distinguish space-occupying lesions from focal fatty infiltration (characterized by isolated areas of fat infiltration) or focal fatty sparing (characterized by isolated areas of normal liver).[45] Magnetic resonance spectroscopy allows a quantitative assessment of fatty infiltration of the liver.[46]

Histologic Findings

Nonalcoholic fatty liver disease is histologically indistinguishable from the liver damage resulting from alcohol abuse. Liver-biopsy features include steatosis, mixed inflammatory-cell infiltration, hepatocyte ballooning and necrosis, glycogen nuclei, Mallory's hyaline, and fibrosis (Fig. 1). The presence of these features, alone or in combination, accounts for the wide spectrum of nonalcoholic fatty liver disease. Portal tracts are relatively spared from inflammation, although children with nonalcoholic fatty liver disease may show a predominance of portal inflammation as opposed to a lobular infiltrate.[10] Mallory's hyaline is notably sparse or absent in children with nonalcoholic fatty liver disease.[10,17,18] In some patients with cirrhosis, the features of steatosis and necroinflammatory activity may no longer be present.[7,8]

A finding of fibrosis in nonalcoholic fatty liver disease suggests more advanced and severe liver injury. According to a number of cross-sectional studies including a total of 673 liver biopsies,[1,3,5-9,11,13-16] some degree of fibrosis is found in up to 66 percent of patients at the time of diagnosis, whereas severe fibrosis (septal fibrosis or cirrhosis) is found in 25 percent and well-established cirrhosis is found in 14 percent.

The combination of steatosis, infiltration by mononuclear cells or polymorphonuclear cells (or both), and hepatocyte ballooning and spotty necrosis is known as nonalcoholic steatohepatitis. Most patients with this type of nonalcoholic fatty liver disease have some degree of fibrosis, whereas Mallory's hyaline may or may not be present. The severity of steatosis can be graded on the basis of the extent of involved parenchyma (Table 2).[41] A system that unifies the lesions of steatosis and necroinflammation into a "grade" and those of the types of fibrosis into a "stage" has recently been proposed (Table 2).[41]

PATHOGENESIS

The pathogenesis of nonalcoholic fatty liver disease has remained poorly understood since the earliest description of the disease. Much current thinking remains hypothetical, since the mechanism or mechanisms are still being worked out. It is not yet understood why simple steatosis develops in some patients, whereas steatohepatitis and progressive disease develop in others; differences in body-fat distribution or antioxidant systems, possibly in the context of a genetic predisposition, may be among the explanations.

A net retention of lipids within hepatocytes, mostly in the form of triglycerides, is a prerequisite for the development of nonalcoholic fatty liver disease. The primary metabolic abnormalities leading to lipid accumulation are not well understood, but they could consist of alterations in the pathways of uptake, synthesis, degradation, or secretion in hepatic lipid metabolism resulting from insulin resistance (Fig. 2A).

Insulin resistance is the most reproducible factor in the development of nonalcoholic fatty liver disease.[63] The molecular pathogenesis of insulin resistance seems to be multifactorial, and several molecular targets involved in the inhibition of insulin action have been identified. These include Rad (ras associated with diabetes),[64] which interferes with essential cell functions (growth, differentiation, vesicular transport, and signal transduction); PC-1 (a membrane glycoprotein that has a role in insulin resistance),[65] which reduces insulin-stimulated tyrosine kinase activity; leptin,[66] which induces dephosphorylation of insulin-receptor substrate-1; fatty acids,[67] which inhibit insulin-stimulated peripheral glucose uptake; and tumor necrosis factor α,[68] which down-regulates insulin-induced phosphorylation of insulin-receptor substrate-1 and reduces the expression of the insulin-dependent glucose-transport molecule Glut4. Insulin resistance leads to fat accumulation in hepatocytes

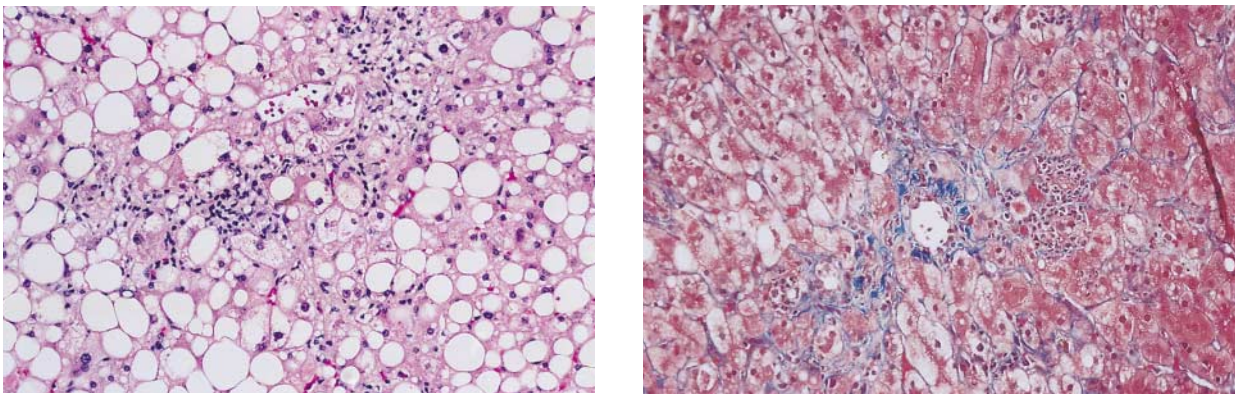
by two main mechanisms: lipolysis and hyperinsulinemia (Fig. 2B).

Clinically significant amounts of dicarboxylic acids, which are potentially cytotoxic, can be formed by microsomal ω-oxidation. This pathway of fatty-acid metabolism is closely related to mitochondrial β-oxidation and peroxisomal β-oxidation (Fig. 2C). Deficiency of the enzymes of peroxisomal β-oxidation has been recognized as an important cause of microvesicular steatosis and steatohepatitis.[69] Deficiency of acyl–coenzyme A oxidase disrupts the oxidation of very-long-chain fatty acids and dicarboxylic acids, leading to extensive microvesicular steatosis and steatohepatitis. Loss of this enzyme also causes sustained hyperactivation of peroxisome-proliferator–activated receptor-α (PPAR-α), leading to transcriptional up-regulation of PPAR-α–regulated genes.[69] PPAR-α has been implicated in promoting hepatic synthesis of uncoupling protein-2, which is expressed in the liver of patients with nonalcoholic fatty liver disease.[49]

Increased intrahepatic levels of fatty acids provide a source of oxidative stress, which may in large part be responsible for the progression from steatosis to steatohepatitis to cirrhosis. Mitochondria are the main cellular source of reactive oxygen species, which may trigger steatohepatitis and fibrosis by three main mechanisms: lipid peroxidation, cytokine induction, and induction of Fas ligand (Fig. 2D).

Patients with steatohepatitis have ultrastructural mitochondrial lesions, including linear crystalline inclusions in megamitochondria.[70] This mitochondrial injury is absent in most patients with simple steatosis and in healthy subjects.[71] Patients with steatohepatitis slowly resynthesize ATP in vivo after a fructose challenge, which causes acute hepatic ATP depletion.[72] This impaired ATP recovery may reflect the mitochondrial injury found in patients with steatohepatitis.[70,71]

Thus, although symptoms of liver disease rarely develop in patients with fatty liver who are obese, have diabetes, or have hyperlipidemia, the steatotic liver may be vulnerable to further injury when challenged by additional insults. This has led to the presumption that progression from simple steatosis to steatohepatitis and to advanced fibrosis results from two distinct events.[73] First, insulin resistance leads to the accumulation of fat within hepatocytes, and second, mitochondrial reactive oxygen species cause lipid



A B

Figure 1. Characteristic Findings of Nonalcoholic Fatty Liver Disease on Liver-Biopsy Specimens.

Panel A shows steatosis (predominantly macrovesicular), an inflammatory infiltrate, Mallory's hyaline, and hepatocyte ballooning (hematoxylin and eosin, ×200). Steatosis is present predominantly as macrovesicular fat, although some hepatocytes may have an admixture of microvesicular steatosis. Fatty infiltration, when mild, is typically concentrated in acinar zone 3, whereas moderate-to-severe fatty infiltration has a more diffuse distribution. The inflammatory infiltrate usually consists of mixed neutrophils and lymphocytes and predominates in zone 3. Ballooning degeneration of hepatocytes results from the accumulation of intracellular fluid and is characterized by swollen cells, typically in zone 3 near the steatotic hepatocytes. Mallory's hyaline is found in about half of adult patients with nonalcoholic fatty liver disease and is usually located in ballooned hepatocytes in zone 3, but it is neither unique nor specific to nonalcoholic fatty liver disease. Panel B shows perivenular fibrosis as well as pericellular and perisinusoidal fibrosis in zone 3 (Masson's trichrome, ×200). The pattern of fibrosis is one of the characteristic features of nonalcoholic fatty liver disease. Collagen is first laid down in the pericellular space around the central vein and in the perisinusoidal region in zone 3. In some areas, the collagen invests single cells in a pattern referred to as "chicken wire" fibrosis, as described in alcohol-induced liver damage. This pattern of fibrosis helps to distinguish nonalcoholic fatty liver disease and alcoholic liver disease from other forms of liver disease in which fibrosis shows an initial portal distribution.

TABLE 2. GRADING AND STAGING THE HISTOPATHOLOGICAL LESIONS OF NONALCOHOLIC FATTY LIVER DISEASE.*

Grading for steatosis

Grade 1: <33% of hepatocytes affected
Grade 2: 33% to 66% of hepatocytes affected
Grade 3: >66% of hepatocytes affected

Grading for steatohepatitis

Grade 1, mild
- Steatosis: predominantly macrovesicular, involves up to 66% of lobules
- Ballooning: occasionally observed; zone 3 hepatocytes
- Lobular inflammation: scattered and mild acute inflammation (polymorphonuclear cells) and occasional chronic inflammation (mononuclear cells)
- Portal inflammation: none or mild

Grade 2, moderate
- Steatosis: any degree; usually mixed macrovesicular and microvesicular
- Ballooning: obvious and present in zone 3
- Lobular inflammation: polymorphonuclear cells may be noted in association with ballooned hepatocytes; pericellular fibrosis; mild chronic inflammation may be seen
- Portal inflammation: mild to moderate

Grade 3, severe
- Steatosis: typically involves >66% of lobules (panacinar); commonly mixed steatosis
- Ballooning: predominantly zone 3; marked
- Lobular inflammation: scattered acute and chronic inflammation; polymorphonuclear cells may be concentrated in zone 3 areas of ballooning and perisinusoidal fibrosis
- Portal inflammation: mild to moderate

Staging for fibrosis

Stage 1: zone 3 perivenular, perisinusoidal, or pericellular fibrosis; focal or extensive
Stage 2: as above, with focal or extensive periportal fibrosis
Stage 3: bridging fibrosis, focal or extensive
Stage 4: cirrhosis

*Adapted from Brunt et al.[41] with the permission of the publisher.

peroxidation, cytokine induction, and the induction of Fas ligand.

DIAGNOSIS

The diagnosis of nonalcoholic fatty liver disease is usually suspected in persons with asymptomatic elevation of aminotransferase levels, radiologic findings of fatty liver, or unexplained persistent hepatomegaly. The clinical diagnosis and liver tests have a poor predictive value with respect to histologic involvement.[74] Imaging studies, although of help in determining the presence and amount of fatty infiltration of the liver, cannot be used to accurately determine the severity of liver damage. The clinical suspicion of nonalcoholic fatty liver disease and its severity can only be confirmed with a liver biopsy.

The diagnosis of nonalcoholic fatty liver disease requires the exclusion of alcohol abuse as the cause of liver disease; a daily intake as low as 20 g in females and 30 g in males may be sufficient to cause alcohol-induced liver disease in some patients (350 ml [12 oz] of beer, 120 ml [4 oz] of wine, and 45 ml [1.5 oz] of hard liquor each contain 10 g of alcohol).[75-77] Other causes, such as viruses, autoimmune responses, metabolic or hereditary factors, and drugs or toxins, should be ruled out. The decision on how extensive the serologic workup should be must be individualized. Specific laboratory test results, along with a number of histologic findings on liver biopsy, make the diagnosis of liver diseases with these other causes straightforward in most cases.

Role of Liver Biopsy

Liver biopsy remains the best diagnostic tool for confirming nonalcoholic fatty liver disease, as well as the most sensitive and specific means of providing important prognostic information. Liver biopsy is also useful to determine the effect of medical treatment, given the poor correlation between histologic damage and the results of liver tests or imaging studies.

Some factors can help to identify patients with nonalcoholic fatty liver disease in whom the liver biopsy may provide the most prognostic information. An age of 45 years or more, the presence of obesity or type 2 diabetes mellitus, and a ratio of aspartate aminotransferase to alanine aminotransferase of 1 or greater are noteworthy indicators of advanced liver fibrosis (Table 3).[14] In the subgroup of overweight patients with a body-mass index over 25, older age, higher body-mass index, and higher levels of alanine aminotransferase and triglycerides are also indicators of more advanced liver fibrosis.[16] In severely obese patients with a body-mass index of more than 35, an index of insulin resistance of more than 5, systemic hypertension, and an elevated alanine aminotransferase level correlate strongly with the presence of steatohepatitis, whereas hypertension and raised levels of alanine aminotransferase and C-peptide suggest the presence of advanced fibrosis.[78]

NATURAL HISTORY

The natural history of nonalcoholic fatty liver disease is not well defined, but it seems to be determined by the severity of histologic damage. In five series, 54 of 257 patients with nonalcoholic fatty liver disease underwent liver biopsy during an average follow-up of 3.5 to 11 years.[6-9,16] Of these patients, 28 percent had progression of liver damage, 59 percent had essentially no change, and 13 percent had improvement or resolution of liver injury. Progression from steatosis to steatohepatitis[26,79] and to more advanced fibrosis[6,7,9,16] or cirrhosis[6-8,16] has been recognized in several cases. Some of the few deaths that occurred among the 257 patients were liver-related, including one from hepatocellular cancer. Thus, many patients with nonalcoholic fatty liver disease have a

relatively benign course, whereas in some others, the disease progresses to cirrhosis and its complications.

Patients found to have pure steatosis on liver biopsy seem to have the best prognosis within the spectrum of nonalcoholic fatty liver disease,[9] whereas features of steatohepatitis or more advanced fibrosis are associated with a worse prognosis.[7,13,16] In one study,[16] progression of liver fibrosis occurred only in patients with necrosis and inflammatory infiltration on liver biopsy. In another study,[13] 36 percent of patients with nonalcoholic fatty liver disease died after a mean follow-up of 8.3 years; liver-related diseases were the second most common cause of death, exceeded only by cancer. There was a trend toward more liver-related deaths among patients with steatohepatitis, which can be explained by the higher prevalence of cirrhosis among these patients.[13] Some data suggest that the coexistence of steatosis with other liver diseases, such as hepatitis C virus infection, could increase the risk of progression of the liver disease.[80]

The natural history of cirrhosis resulting from nonalcoholic fatty liver disease has not been completely defined. In a recent study,[81] only 2.9 percent of 546 liver-transplantation procedures performed in a single center were for end-stage steatohepatitis. This suggests that although nonalcoholic fatty liver disease is common, only a minority of patients will require liver transplantation.

One of the shortcomings of studies on the natural history of nonalcoholic fatty liver disease[6-9,13,16] is that patients who subsequently underwent liver biopsy and who underwent long-term follow-up were highly selected. Population-based studies will better define the natural history of this condition.

MANAGEMENT

Associated Conditions

In patients with diabetes mellitus or hyperlipidemia, good metabolic control is always recommended, but it is not always effective in reversing nonalcoholic fatty liver disease. Improvement in liver-test

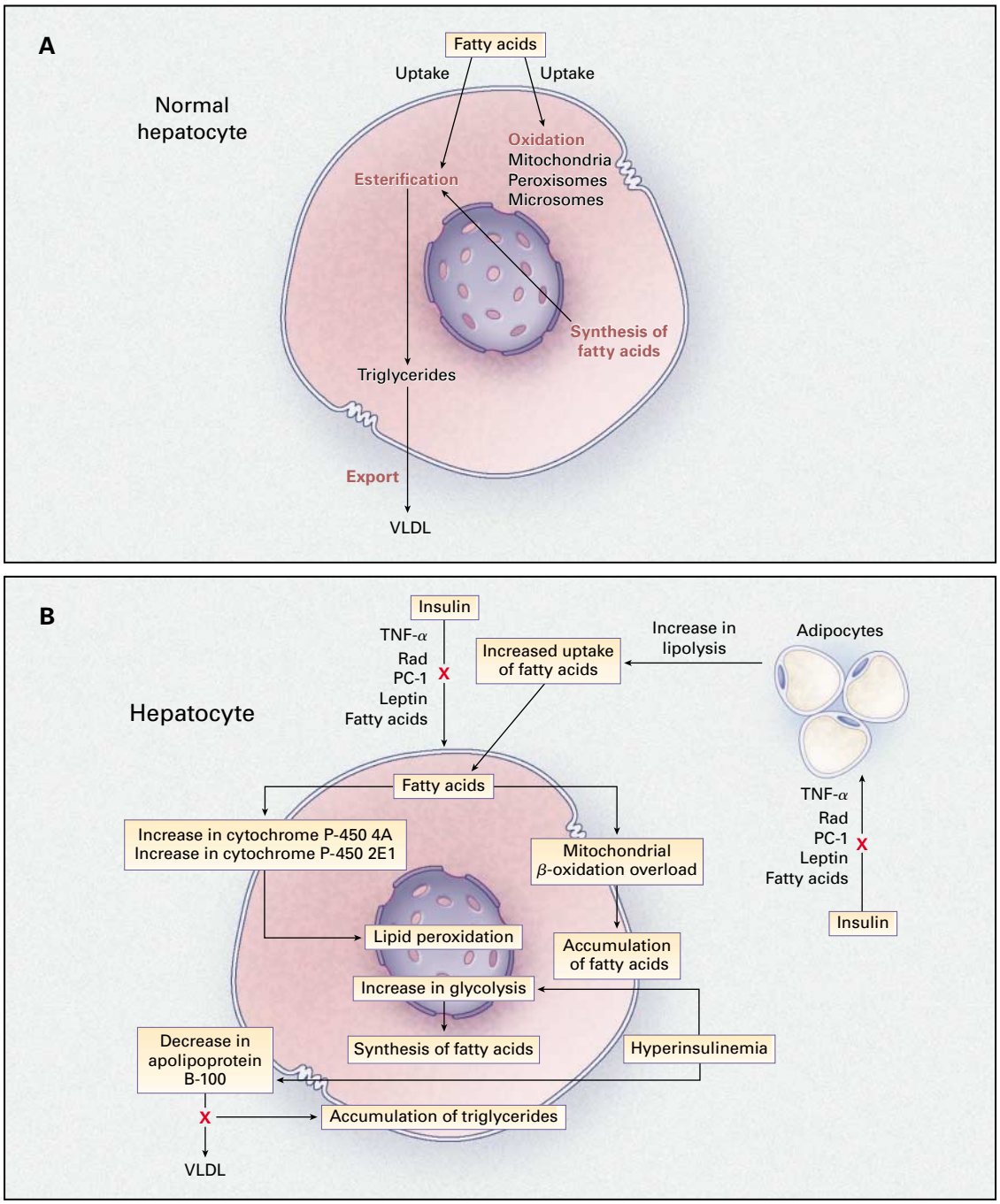
Figure 2 (pages 1227 and 1228). Possible Mechanisms of Pathogenesis of Nonalcoholic Fatty Liver Disease.

As shown in Panel A, hepatic fatty acids are normally esterified into triglycerides, some of which are exported out of hepatocytes as very-low-density lipoproteins (VLDL). The increased level of lipids, mostly in the form of triglycerides, within hepatocytes in patients with nonalcoholic fatty liver disease results from an imbalance between the enzyme systems that promote the uptake and synthesis of fatty acids and those that promote the oxidation and export of fatty acids.

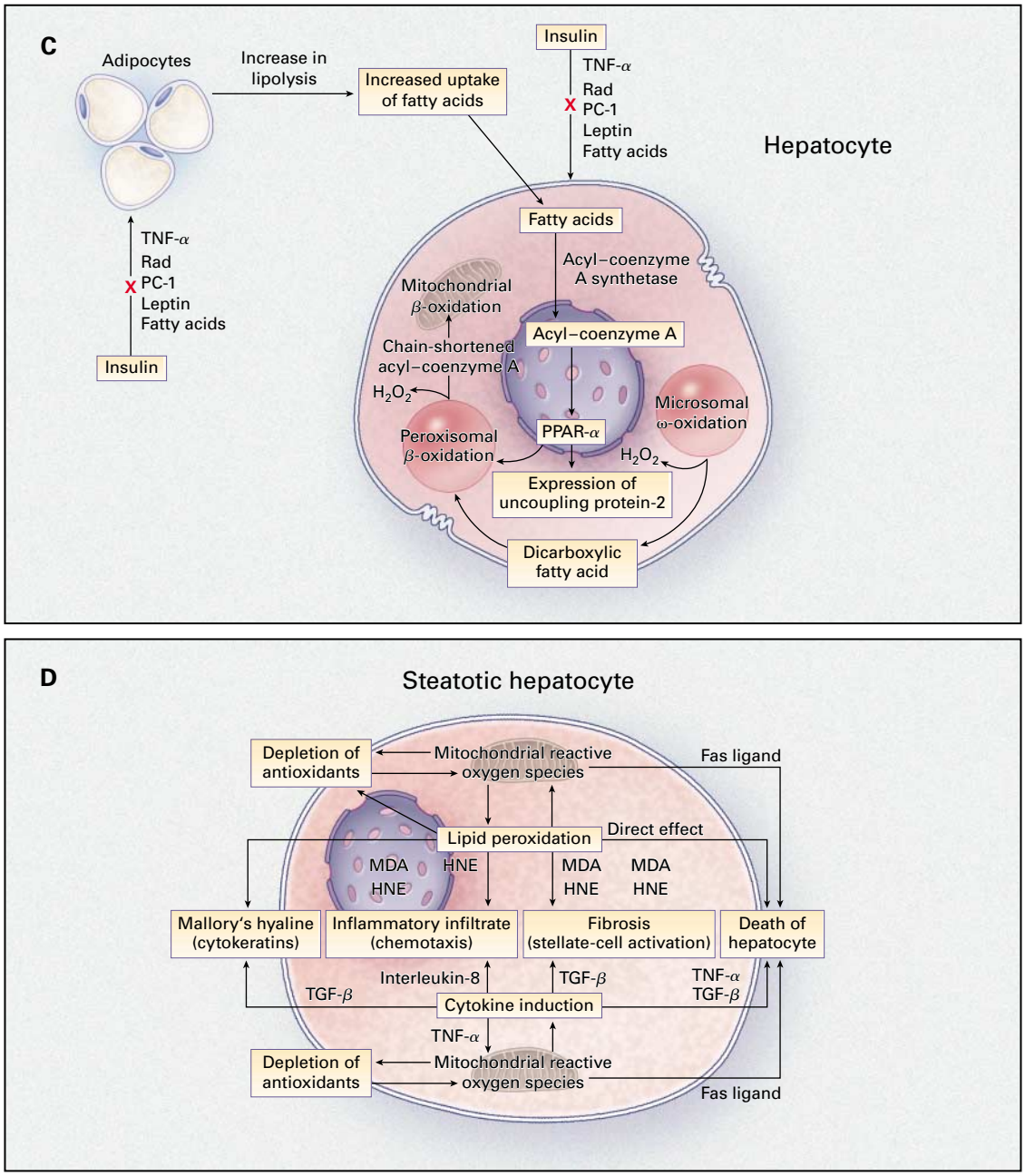
In Panel B, insulin resistance (owing to inhibition of tumor necrosis factor α [TNF-α], Rad, PC-1, eptin, and fatty acids) leads to the accumulation of fat in hepatocytes by two main mechanisms: lipolysis, which increases circulating fatty acids, and hyperinsulinemia. Increased uptake of fatty acids by hepatocytes leads to mitochondrial β-oxidation overload, with the consequent accumulation of fatty acids within hepatocytes. Fatty acids are substrates and inducers of the microsomal lipoxygenases cytochrome P-450 2E1 and 4A.[47,48] The level of cytochrome P-450 2E1 is invariably increased in the liver of patients with steatohepatitis and may result in the production of free oxygen radicals capable of inducing lipid peroxidation of hepatocyte membranes.[47] Extensive lipid peroxidation is also observed in transgenic mice in which the cytochrome P-450 2E1 gene has been knocked out, suggesting that cytochrome P-450 4A enzymes may have the principal role.[48] Hyperinsulinemia resulting from insulin resistance increases the synthesis of fatty acids in hepatocytes by increasing glycolysis and favors the accumulation of triglycerides within hepatocytes by decreasing hepatic production of apolipoprotein B-100.

Panel C shows the relation between microsomal ω-oxidation, peroxisomal β-oxidation, and mitochondrial β-oxidation, as well as the regulatory role of peroxisome-proliferator–activated receptor α (PPAR-α) ligand. Microsomal ω-oxidation of fatty acids generates dicarboxylic fatty acids, which are further degraded by peroxisomal β-oxidation. Peroxisomal β-oxidation generates chain-shortened acyl–coenzyme A. Very-long-chain fatty acids are converted to acyl–coenzyme A by the action of acyl–coenzyme A synthetase. Acyl–coenzyme A serves as a substrate for peroxisomal oxidation, but if left unmetabolized, it functions as a PPAR-α ligand. PPAR-α controls the induction of genes involved in microsomal, peroxisomal, and mitochondrial fatty-acid oxidation systems in liver, and it may also promote hepatic synthesis of uncoupling protein-2.[49] The role of this protein in the pathogenesis of nonalcoholic fatty liver disease remains uncertain. It may help inhibit hepatocyte apoptosis, but it may also increase the vulnerability of fatty hepatocytes to subsequent injury when exposed to secondary insults such as endotoxin or TNF-α.[49-51]

In Panel D, mitochondrial reactive oxygen species promote progression from steatosis to steatohepatitis and fibrosis by three main mechanisms: lipid peroxidation, cytokine induction, and Fas ligand induction. Reactive oxygen species trigger lipid peroxidation, which causes cell death and releases malondialdehyde (MDA) and 4-hydroxynonenal (HNE).[52] MDA and HNE cause cell death; cross-link proteins, leading to the formation of Mallory's hyaline[53]; and activate stellate cells, promoting collagen synthesis.[54] HNE has chemotactic activity for neutrophils, promoting tissue inflammation.[55] Reactive oxygen species also induce the formation of the cytokines TNF-α, transforming growth factor β (TGF-β), and interleukin-8. TNF-α and TGF-β cause caspase activation and hepatocyte death.[56,57] TGF-β activates collagen synthesis by stellate cells[54] and activates tissue transglutaminase, which cross-links cytoskeletal proteins, promoting the formation of Mallory's hyaline. Interleukin-8 is a potent chemoattractant for human neutrophils.[58] The TNF-α induced by reactive oxygen species further impairs the flow of electrons along the respiratory chain in mitochondria.[59] Mitochondrial reactive oxygen species can deplete hepatic antioxidants, allowing accumulation of more reactive oxygen species.[60,61] Mitochondrial reactive oxygen species cause expression of the Fas ligand in hepatocytes, which normally express the membrane receptor Fas.[62] The Fas ligand on one hepatocyte can then interact with Fas on another hepatocyte, causing fractional killing.



results is almost universal in obese adults[26,79,82-84] and children[17,29,85] after weight reduction. The degree of fatty infiltration usually decreases with weight loss in most patients, although the degree of necroinflammation and fibrosis may worsen.[26,79,83,84,86,87] The rate of weight loss is important and may have a critical role in determining whether liver histologic findings will improve or worsen. In patients with a high degree of fatty infiltration, rapid weight loss may promote necroinflammation, portal fibrosis, and bile stasis.[26,79,86] A weight loss of about 500 g per week in children[29,85] and 1600 g per week in adults[79] has



been advocated. Nevertheless, the most effective rate and degree of weight loss still have to be established.

Drug Therapy

No medications have been proved to directly reduce or reverse liver damage independently of weight loss, but such medications would be desirable. Only small pilot studies lasting one year or less have been reported to date. Gemfibrozil,[88] vitamin E (α-tocopherol),[89] and metformin[90] have been shown to improve liver-test results. Ursodiol,[91] betaine,[92] vitamin E,[93] and the thiazolidinedione troglitazone[94] led to improvement in liver-test results as well as histologic findings. These medications deserve further evaluation in carefully controlled clinical trials that have sufficient statistical power and include clinically rel-

TABLE 3. ADJUSTED ODDS RATIOS FOR SEVERE FIBROSIS (SEPTAL FIBROSIS OR CIRRHOSIS).*

RISK FACTOR	ODDS RATIO (95% CI)
Age ≥45 yr	5.6 (1.5–21.7)
Obesity (body-mass index ≥30)	4.3 (1.4–13.8)
Aspartate aminotransferase:alanine aminotransferase ratio >1	4.3 (1.5–12)
Type 2 diabetes mellitus	3.5 (1.2–9.8)

*Adapted from Angulo et al.[14] with the permission of the publisher. CI denotes confidence interval.

evant end points. Troglitazone has been removed from the market because of its potential hepatotoxicity.

General Recommendations

An attempt at gradual weight loss along with appropriate control of serum glucose and lipid levels is a useful first step. Perhaps these should be the only treatment recommendations for patients with nonalcoholic fatty liver disease with pure steatosis and no evidence of necroinflammation or fibrosis.

Since most patients who have problems from nonalcoholic fatty liver disease have steatohepatitis,[7,13,16] treatment is more likely to be aimed at those with steatohepatitis. Patients with steatohepatitis, particularly those with fibrosis on liver biopsy, should be monitored closely, with more careful metabolic control, and be offered enrollment in clinical trials.

Many patients with cirrhotic-stage nonalcoholic fatty liver disease have coexisting conditions that reduce the usefulness of liver transplantation. Nevertheless, for the patient with decompensated cirrhosis, liver transplantation is a potential therapeutic alternative. Nonalcoholic fatty liver disease, however, may recur in the allograft[81] or develop after liver transplantation for cryptogenic cirrhosis.[95]

CONCLUSIONS

Nonalcoholic fatty liver disease affects a large proportion of the world's population. Insulin resistance and oxidative stress have critical roles in the pathogenesis of nonalcoholic fatty liver disease. Liver biopsy remains the most sensitive and specific means of providing important prognostic information. Simple steatosis may have the best prognosis within the spectrum of nonalcoholic fatty liver disease, but it has the potential to progress to steatohepatitis, fibrosis, and even cirrhosis. No effective medical therapy is currently available for all patients with nonalcoholic fatty liver disease. Weight reduction, when achieved and sustained, may improve the liver disease. Pharmacologic therapy aimed at the underlying liver disease holds promise. However, questions remain regarding the use of drug therapy and the effect of recommended dietary measures. Liver transplantation is a therapeutic alternative for some patients with decompensated, end-stage nonalcoholic fatty liver disease, but nonalcoholic fatty liver disease may recur or develop after liver transplantation.

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