

Nonalcoholic Fatty Liver Disease (NAFLD): A Comprehensive Review

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Nonalcoholic fatty liver disease (NAFLD) is defined as fatty infiltration of the liver exceeding 5% to 10% by weight. It is a spectrum of disorders ranging from simple fatty liver (steatosis without liver injury), nonalcoholic steatohepatitis (steatosis with inflammation), and fibrosis/cirrhosis that resembles alcohol-induced liver disease but which develops in individuals who are not heavy drinkers. NAFLD is likely the most common cause of chronic liver disease in many countries. NAFLD may also potentiate liver damage induced by other agents, such as alcohol, industrial toxins and hepatatrophic viruses.

The lack of specific and sensitive noninvasive tests for NAFLD limits reliable detection of the disease. It is often diagnosed on a presumptive basis when liver enzyme elevations are noted in overweight or obese individuals without identifiable etiology for liver disease, or when imaging studies suggest hepatic steatosis.

NAFLD is now considered to be a component of the insulin resistance syndrome (metabolic syndrome X). Controversy exists relative to optimal recognition, diagnosis and management of these conditions, and treatment recommendations are evolving.

Fatty liver disease that develops in the absence of alcohol abuse is recognized increasingly as a major health burden. Estimates based on imaging and autopsy studies suggest that about 20% to 30% of adults in the United States and other Western countries have excess fat accumulation in the liver. Approximately 10% of these individuals, or fully 2% to 3% of adults, are estimated to meet current diagnostic criteria for nonalcoholic steatohepatitis (NASH). Sustained liver injury leads to progressive fibrosis and cirrhosis in up to one third of those with NASH, which may be a cause of cryptogenic cirrhosis. NASH is now a significant health issue for obese children, leading to cirrhosis in some.

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THE SPECTRUM OF NAFLD

The diagnosis of NAFLD is based upon noninvasive and invasive tests, with liver biopsy being the most definitive modality. Hepatic steatosis is at the lower end of the spectrum of NAFLD clinical severity. Predominantly large (macro-) and occasionally small (micro-) vesicles of fat, predominately triglycerides, accumulate within hepatocytes without causing appreciable hepatic inflammation, liver cell death, or scarring. At the mid-range of the severity spectrum is steatohepatitis (nonalcoholic steatohepatitis, or NASH), which is an intermediate form of liver damage superimposed upon a background of he-

Table 1. Nomenclature of Fatty Disorders of the Liver

Histologic nomenclature

1. Fatty liver (grade)
2. Steatohepatitis
 - a. Grade: degree of necroinflammatory activity
 - b. Stage: degree of fibrosis

patic steatosis. Steatohepatitis is characterized by the appearance of focal hepatic inflammation and hepatocyte necrosis and death. At the highest end of the severity spectrum is cirrhosis. By the time this degree of architectural distortion develops, hepatic steatosis has often disappeared. Because all of these histologic features also occur in alcohol- or drug-induced fatty liver diseases, liver biopsy cannot reliably distinguish among the various causes of this entity.

NOMENCLATURE OF FATTY DISORDERS OF THE LIVER

A complete diagnosis of fatty liver disease (ideally) should define the histology, including the grade (severity) and stage (degree of fibrosis) of the disease as well as its clinical association (Tables 1 and 2).

Traditionally, fatty disorders of the liver have been classified as alcoholic or nonalcoholic. NAFLD includes both nonalcoholic fatty liver and NASH. NAFLD is associated with numerous etiologies (Table 2). The term “nonalcoholic fatty liver disease” renders the condition heterogeneous in terms of etiology, natural history, as well as response to therapy. This makes the condition harder to study and is therefore unsatisfactory. There is currently no consensus on the best way to classify fatty disorders of the liver.

HISTOLOGIC CRITERIA FOR THE DIAGNOSIS OF FATTY LIVER AND STEATOHEPATITIS

The principal histologic feature of NAFLD is the presence of macrovesicular fatty change in hepatocytes with displacement of the nu-

cleus to the edge of the cell. The original descriptions of steatohepatitis included the presence of Mallory bodies, ballooning degeneration, predominant lobular neutrophilic inflammation, and Rappaport zone III perisinusoidal fibrosis. Now it is realized that only some of these features may be present in a given patient. Mallory bodies are less frequently seen in NASH compared with alcoholic steatohepatitis and may even be absent. Also, in many individuals, atypical features (eg, predominantly lymphocytic inflammation or portal fibrosis) are present. It is not known whether these histologic patterns represent different stages of steatohepatitis or separate clinicopathologic conditions with overlapping histologic expression. Despite an attempt to standardize the histologic diagnostic criteria for steatohepatitis during a workshop at the National Institutes of Health, no consensus exists on this subject.

The best definition of NASH remains unsettled, since there is significant diversity of opinion among experts regarding the necessity and character of specific findings. A proposed NAFLD classification system correlates certain histologic features with the long-term prognosis. In 1999, researchers introduced the 4-tiered Matteoni system (Table 3) to describe the stages of NASH.¹

Classes 3 and 4 NAFLD in Matteoni’s system are similar and might be considered as a single group constituting NASH. These classes describe NAFLD that has progressed to the far more serious NASH, in which varying degrees of fibrosis and/or cirrhosis develop and balloon cells or Mallory’s bodies appear. Class 2 NAFLD is more controversial; it may be benign and includes relatively more men often with a normal body mass index.

In another study, Brunt et al scored a total of 10 findings to develop a grading and staging system for NASH.² These included hepatic macrovesicular steatosis, hepatocellular ballooning, intra-acinar inflammation, portal tract inflammation, Mallory’s hyaline, acidophil bodies, glycogen nuclei, lipogranulomas, and hepatocellular iron. Each of these was scored separately. Three parameters of he-

Table 2. Conditions Associated With Steatohepatitis¹⁹

All conditions except alcoholism are usually referred to as nonalcoholic steatohepatitis (NASH).

1. Alcoholism
2. Insulin resistance
 - a. Syndrome X
 - i. Obesity
 - ii. Diabetes
 - iii. Hypertriglyceridemia
 - iv. Hypertension
 - b. Lipoatrophy
 - c. Mauriac syndrome
3. Disorders of lipid metabolism
 - a. Abetalipoproteinemia
 - b. Hypobetalipoproteinemia
 - c. Andersen's disease
 - d. Weber-Christian syndrome
4. Total parenteral nutrition
5. Severe weight loss
 - a. Jejunioileal bypass
 - b. Gastric bypass (much less common than after jejunioileal bypass)
 - c. Severe starvation
6. Iatrogenic/drugs (see Secondary Causes of Steatosis, Table 5)
7. Refeeding syndrome
8. Toxic exposure
 - a. Environmental
 - b. Workplace

Table 3. Matteoni's Classification of the Stages of NAFLD/NASH¹

Class 1: Simple steatosis without inflammation or fibrosis
Class 2: Steatosis with lobular inflammation but without fibrosis
Class 3: Additional presence of ballooned hepatocytes
Class 4: Presence of either Mallory's hyaline or fibrosis

patic fibrosis were scored: perisinusoidal fibrosis, portal fibrosis, and bridging fibrosis. Based on these, the necroinflammatory activity was graded as mild, moderate or severe (Table 4).

PATHOGENESIS OF NAFLD

The pathogenesis of NAFLD has not been clearly established. Both "nature" (ie, genetic control of inflammatory responses) and "nurture" (ie, epigenetic causes of oxidative stress/inflammation and health-related be-

havior regarding lifestyle) contribute to NAFLD.

The pathogenesis of NAFLD has been hypothesized to be a 2-stage process. In the first stage, fatty acids accumulate in hepatocytes leading to steatosis. The development of steatosis is associated with obesity, particularly central abdominal adiposity, and insulin resistance. Hepatic steatosis predisposes to liver injury in the second stage, which is characterized by necrosis, inflammation and fibrosis. It has been proposed that the primary mediator of this second stage is oxidative stress. Pro-oxidants, such as iron, would be expected to worsen liver injury. Conversely, antioxidants, such as certain vitamins and minerals, would be expected to protect against liver injury.

Stress Response

Insulin resistance (metabolic syndrome X) and NAFLD are related to "stress." Dr. Bruce

Table 4. Grading and Staging of NAFLD According to Brunt et al²

Grading	
Macrovesicular steatosis	
Grade 0:	None
Grade 1:	Up to 33%
Grade 2:	33%–66%
Grade 3:	>66%
Necroinflammatory activity	
Grade 1:	Mild
	Steatosis up to 66%, occasional ballooned hepatocyte (mainly zone III), scattered intra-acinar neutrophils (PMN) ± lymphocytes, no or mild portal inflammation
Grade 2:	Moderate
	Steatosis of any degree, obvious zone III ballooning degeneration, intra-acinar PMNs, zone III perisinusoidal fibrosis may be present, mild to moderate, portal and intra-acinar inflammation
Grade 3:	Severe
	Panacinar steatosis, widespread ballooning, intra-acinar inflammation, PMNs associated with ballooned hepatocytes, mild to moderate portal inflammation
Staging	
Stage 1:	Zone III perisinusoidal/pericellular fibrosis, focally or extensively present
Stage 2:	Zone III perisinusoidal/pericellular fibrosis with focal or extensive periportal fibrosis
Stage 3:	Zone III perisinusoidal/pericellular fibrosis and portal fibrosis with focal or extensive bridging fibrosis
Stage 4:	Cirrhosis

S. McEwen from Rockefeller University has developed a new way of conceptualizing and understanding the stress response.³ When stressors (triggers) represent a real or perceived threat to the neurobiological balance (homeostasis) of the person, physiological and behavioral responses are triggered in order to achieve adaptation and survival in the short run (ie, allostasis, or “good stress”). The protective and restorative allostatic processes of the body are mediated through the autonomic nervous system, the hypothalamic-pituitary-adrenal (HPA) axis and the cardiovascular, metabolic and immune systems. However, over longer periods of time, these same response systems that are designed to protect and restore can be damaging and can cause or exacerbate symptoms, disease and illness (ie, allostatic load, or “bad stress”). See Figure 1.

The perception of stress is influenced by one’s experiences, genetics and behavior. When the brain perceives an experience as stressful, physiologic and behavioral responses are initiated leading to allostasis and adaptation. Over time, allostatic load can accu-

mulate, and overexposure to and/or mismanagement of mediators of neural, endocrine, and immune stress can have adverse effects on various organ systems leading to disease.

Dysregulation of the central stress response system related to allostatic load contributes to the development of a variety of diseases and illnesses including hypertension, atherosclerosis, central obesity, diabetes, and the insulin resistance syndrome (metabolic syndrome X).²⁰ Gastrointestinal diseases and illnesses adversely impacted by allostatic load include non-alcoholic fatty liver disease (also associated with the insulin resistance syndrome), gastroesophageal reflux disease (GERD), peptic ulcer disease, inflammatory bowel disease and functional gastrointestinal disorders (FGID).

NATURAL HISTORY OF NAFLD

Only limited natural history data are available concerning the spectrum of histologic lesions seen in macrovesicular fatty disorders of the liver not associated with the use of alcohol. It is generally believed that there are

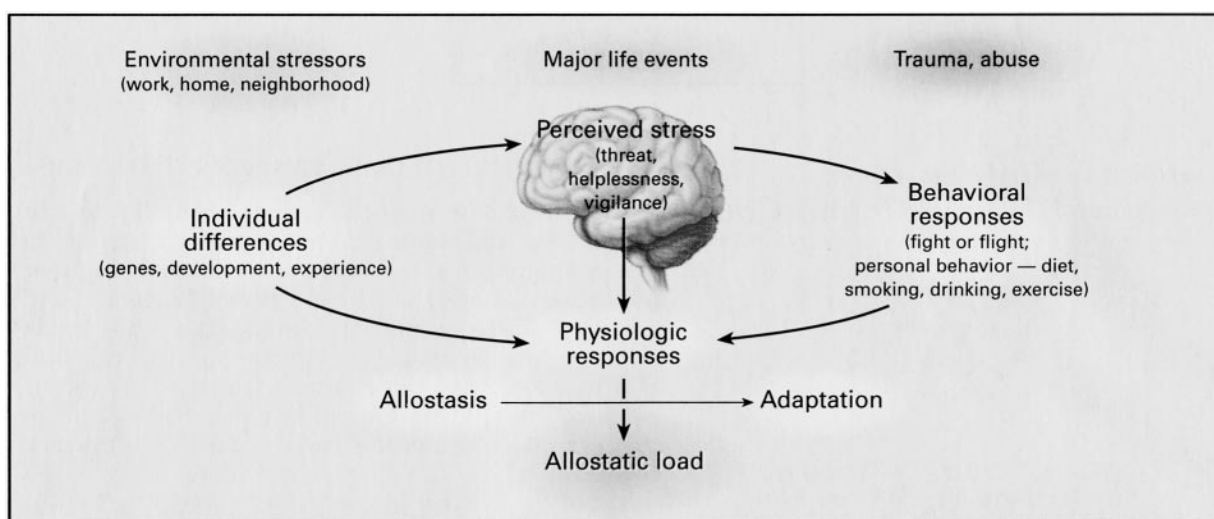


Figure 1. *The Stress Response and Development of Allostatic Load* (McEwen B. N Engl. J Med. 1998;338:171–179. Republished with permission. Copyright © 1998 Massachusetts Medical Society. All rights reserved.)

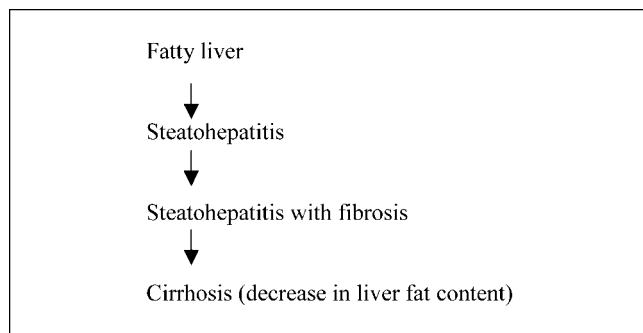


Figure 2. *Stages in the Progression of NAFLD.*

several distinct histologic states in the natural history of these disorders that indicate progression of the lesion (Figure 2). These include a fatty liver alone, steatohepatitis, steatohepatitis with fibrosis, and eventually cirrhosis. It has also been noted that fatty change may disappear following development of cirrhosis.

Cross-sectional studies of nonalcoholic fatty liver indicate that most subjects have fatty liver alone. It is currently believed that it is rare for such patients to progress to steatohepatitis or steatosis with fibrosis over time. In a recent study, only 2.9% of 546 liver-transplantation procedures performed in a single center were for end-stage steatohepatitis.⁴ Even though NAFLD is common, only a minority of patients will require liver transplantation.

Although the natural history of NAFLD is

not well defined, it seems to be determined by the severity of liver damage. At this time, few patients have been observed prospectively in order to document the natural history of NASH, which is generally considered to be a clinically stable disorder with a much better prognosis than alcoholic hepatitis. In 5 series, 54 of 257 patients with NAFLD underwent liver biopsy during an average follow-up of 3.5 to 11 years. Twenty-eight percent had progression of liver damage, 59% had essentially no change, and 13% had improvement or resolution of liver injury. Progression from steatosis to steatohepatitis and to more advanced fibrosis or cirrhosis 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 NAFLD have a relatively benign course, whereas in some others, the disease progresses to cirrhosis and its complications.⁹

At the time of initial presentation, about 30%–40% of patients with NASH have advanced fibrosis, whereas 10%–15% have established cirrhosis. By multivariate analysis, increasing age, obesity, and diabetes were noted to be independent predictors of bridging fibrosis or cirrhosis. Another recent study has confirmed the relationship between the degree of obesity and the likelihood of advanced fibrosis.

Patients found to have pure steatosis on liver biopsy seem to have the best prognosis within the spectrum of NAFLD. Features of steatohepatitis or more advanced fibrosis are associated with a worse prognosis. With the exception of the histologic features discussed here, there are no clinical or laboratory features that can predict progression in any given patient.

According to Arun J. Sanyal, MD, chairman of the Division of Gastroenterology and Nutrition at Virginia Commonwealth University School of Medicine, Classes 1 and 2 NAFLD appear to be stable over time and even reversible with weight loss, diet modification, and for diabetics sound disease management.⁵ The long-term prognosis for patients with Classes 1 and 2 NAFLD is usually good, especially if the underlying causes are addressed. Early-stage NAFLD could conceivably progress to NASH, but the transition is probably unusual, while the speed of liver deterioration remains unknown. Dr. Sanyal suspects that once NASH emerges bridged with fibrosis or cirrhosis, mortality rates reach as high as 20% at 10 to 15 years following diagnosis; however, he cautions that no firm data back up this generalized estimate.

A shortcoming of studies on the natural history of NAFLD is that patients who subsequently underwent liver biopsy and long-term follow-up were highly selected and may have altered health-related behavior. Population-based studies will be necessary to better define the natural history of NAFLD.

DIFFERENTIAL DIAGNOSIS OF NAFLD

Alcohol and NAFLD

“Nonalcoholic” is inherent to defining NAFLD and NASH, since it refers to a threshold at which the liver abnormality becomes alcohol related. The distinction of alcoholic vs nonalcoholic is not sharp and is controversial. There are no published and universally accepted threshold levels of alcohol intake that separate alcoholic fatty liver disease from NAFLD. Many centers accept up to 20–40 grams of ethanol per day in men

and 20 grams per day in women, while others have utilized a cut-off level of 10 grams of ethanol per day or less. One study has reported that limited alcohol intake is protective against NASH (as well as diabetes), and there is evidence for health benefits derived from modest alcohol ingestion.⁹ The threshold issue will not be easily resolved. In a recent summary of NASH, a reasonable compromise was proposed: 20 grams of ethanol per day. This cut-off level is well below the traditional threshold for alcohol-induced liver disease (40 to 60 grams of ethanol per day). Thus, it is generally believed that a fatty liver does not develop with alcohol consumption levels <20 g/day.

Determination of an individual’s alcohol consumption is easier said than done. Assessment of the amount of alcohol consumed from that reported by patients is notoriously inaccurate. Questioning of family members may be useful in some instances.

The shortcomings of this approach have led to the development of direct and surrogate markers of alcohol consumption. These include serum gamma-glutamyltransferase levels, mean corpuscular volume, aminotransferase (AST) levels, AST/alanine aminotransferase (ALT) ratio, mitochondrial AST levels, and desialylated transferrin levels. The first 4 tests are both widely available and relatively inexpensive. Unfortunately, these lack both sensitivity and specificity, and neither the negative nor positive predictive values are high enough to be clinically useful. The clinical utility of the other markers has not been examined outside of a few limited clinical studies.

Secondary Causes of Steatosis

NAFLD is differentiated from steatosis, with or without hepatitis, resulting from secondary causes, since these conditions have different pathogeneses and clinical outcomes. Steatosis may be either macrovesicular (mainly related to imbalance in the hepatic synthesis and export of lipids) or microvesicular (mainly related to defects in mitochondrial

function). Rarely, phospholipidosis occurs (mainly by accumulation of phospholipids in lysosomes). See Table 5.

COEXISTING DISORDERS

Most liver disorders are associated with abnormalities of biochemical liver tests and require differentiation from NAFLD. Furthermore, NAFLD is so prevalent that it often coexists with other liver disorders. It is particularly important to identify benign and malignant liver lesions, drug-induced hepatitis, chronic viral hepatitis B and C, hemochromatosis, and autoimmune hepatitis, since potentially effective therapies are available.

The presence of hepatitis C was originally believed to constitute an exclusion criterion for the diagnosis of NASH. However, some with hepatitis C clearly have histologic evidence of a classic steatohepatitis rather than the predominantly portal lymphocytic infiltrate with mild to moderate steatosis seen in hepatitis C. In such cases, the presence of 2 diagnoses (ie, hepatitis C and NASH) may be considered. It is important to exclude genetic hemochromatosis if iron abnormalities are identified. (See Liver Enzymes: Ferritin section)

CLINICAL ASSESSMENT

Symptoms

As with many other types of chronic liver disease, most patients with NAFLD in cross-sectional studies are asymptomatic. The liver disease is either discovered incidentally during routine laboratory examination or workup of conditions such as hypertension, diabetes, or morbid obesity. Elevated ALT levels or sonographic evidence of fatty liver is sometimes noted during workup of suspected gallstone disease.

Only limited data on symptomatology are available from longitudinal studies, and both the likelihood of developing symptoms over time as well as the predictors of future development of symptoms are not known. Most patients with NAFLD are asymptomatic.

When symptoms occur, they are usually nonspecific. Fatigue is probably the most commonly reported symptom and does not correlate well with the severity of the histologic lesion. Another common symptom is right upper quadrant discomfort, which is typically of a vague, nondescript aching character.

A smaller fraction of patients experience symptoms indicative of more serious liver disease and may develop pruritus, anorexia and nausea.

Signs

There are no pathognomonic signs of NASH. Obesity is the most common abnormality on physical examination and is present in 30%–100% of patients in various cross-sectional studies. The most common finding of liver disease is hepatomegaly, which has been reported in up to 50% of subjects in different studies. A smaller percentage of patients have stigmata of chronic liver disease. Of the various stigmata known, the presence of spider nevi and palmar erythema are most common. Jaundice, edema, asterixis, and signs of portal hypertension occur in those with advanced cirrhosis. Muscle wasting may occur as the liver disease becomes more advanced but is often underestimated due to edema and preexisting obesity.

LIVER ENZYMES

Aminotransferases

Clinical suspicion of a diagnosis of NAFLD is most commonly triggered by the discovery of abnormal liver blood test values, particularly aminotransferases (AST and ALT). However, the presence, degree, and pattern of aminotransferase elevation are nonspecific and do not provide an etiologic diagnosis. Even when the index of suspicion for NASH is high (eg, in an obese, diabetic individual), the aminotransferase levels do not distinguish between fatty liver alone and NASH.

Liver enzymes can be normal, at least intermittently, in those with any given histologic stage of NAFLD. Thus, the presence of nor-

Table 5. Secondary Causes of Steatosis¹⁹

Nutritional (predominantly macrovesicular steatosis)

- Protein-calorie malnutrition
- Starvation
- Total parenteral nutrition
- Rapid weight loss
- Bariatric surgery

Drugs

This is a partial list; some drugs also produce inflammation. Drug-induced steatosis may have no clinical consequences (eg, corticosteroids) or can result in cirrhosis (eg, methotrexate and amiodarone).

- Glucocorticoids
- Synthetic estrogens
- Aspirin
- Calcium-channel blockers (weak association)
- Amiodarone (hepatic phospholipidosis)
- Tamoxifen
- Tetracycline
- Methotrexate
- Perhexiline maleate (hepatic phospholipidosis)
- Valproic acid
- Cocaine
- Antiviral drugs
 - Zidovudine
 - Didanosine
 - Fialuridine

Metabolic or genetic disorders (rare)

- Lipodystrophy
- Dysbetalipoproteinemia
- Weber-Christian disease
- Wilson's disease
- Wolman's disease
- Cholesterol ester storage disease
- Acute fatty liver of pregnancy

Other

- Inflammatory bowel disease
- Small bowel diverticulosis with bacterial overgrowth
- Human immunodeficiency virus infection
- Environmental hepatotoxins
 - Phosphorus
 - Petrochemicals
 - Toxic mushrooms
 - Organic solvents
- Bacillus cereus* toxins

mal or near-normal aminotransferase values does not exclude significant underlying liver damage.

The degree of aminotransferase enzyme elevation is usually mild and is most typically less than 1.5 times normal, ranging up to 4 times normal. Levels seldom exceed 10 times normal. The degree of aminotransferase ele-

vation cannot be used as a predictive factor. ALT values do not correlate with the degree of steatosis or fibrosis, and significant liver disease may exist with liver enzymes in the normal range among NAFLD patients.

Although the ALT levels are higher than AST levels in most instances, the AST level may be higher than the ALT level, especially

in the presence of cirrhosis or when underlying alcoholism is present. However, the AST/ALT ratio is almost never greater than 2 in NAFLD. In those patients with elevated ALT levels, the elevation is usually persistent although the precise value may fluctuate. Less commonly, the serum ALT level remains persistently normal.

It is not clear if ALT should be used alone or whether AST and ALT or other combinations of liver tests should be used. There is also debate regarding whether cutoffs should be different for men and women. Furthermore, the level of elevation that is considered to be abnormal varies widely and has recently been brought into question.^{6,7}

Relative to the controversy over the sensitivity of aminotransferase levels, it is clear that more acceptable and accurate methods for the noninvasive recognition and diagnosis of liver disease in general and NAFLD in particular are needed. While most individuals with NAFLD have abnormal liver chemistries, it is clear that significant liver disease can exist with liver enzymes in the normal range among NAFLD patients.

Gamma-Glutamyltransferase (GGT)

Although GGT levels may be elevated, there are little data on the frequency and degree of elevation. The degree of elevation tends to be lower than that seen with alcoholic liver injury.

Alkaline Phosphatase

The alkaline phosphatase level may also be variably elevated up to twice the upper limit of normal.

Ferritin

Elevated serum ferritin levels may be a clue that nonalcoholic steatohepatitis (NASH) is present, because elevated ferritin with or without increased transferrin saturation has been described in many NASH patients who do not have C282Y or H63D mutations in the HFe gene (ie, genetic hemochromatosis). Ele-

vated serum ferritin values are found in half of patients with NAFLD. Increased transferrin saturation is found in 6% to 11% of patients. The hepatic iron index and the hepatic iron level are usually within the normal range.

Hepatic Synthetic Function Tests (Albumin, Prothrombin Time, Serum Bilirubin)

As expected, measures of hepatic functional capacity do not become abnormal until cirrhosis and liver failure develop. The serum albumin level and prothrombin time become abnormal before the serum bilirubin level does. In a diabetic subject with NASH, isolated hypoalbuminemia may also occur due to proteinuria related to diabetic nephropathy.

Complete Blood Count (CBC)

Hematological parameters are usually normal unless cirrhosis and portal hypertension lead to hypersplenism. Thrombocytopenia, with or without detectable splenomegaly, is a common clinical clue that cirrhosis (complicated by hypersplenism) has developed. Alcoholism associated bone marrow suppression can result in reversible thrombocytopenia that can be mistaken for hypersplenism.

ABDOMINAL IMAGING

Abdominal imaging studies are often ordered instead of liver biopsy to confirm the clinical suspicion of NAFLD. The rationale here is the avoidance of the risks associated with an invasive procedure. (See Liver Biopsy section).

The presence of fat in the liver can be diagnosed in many cases using various imaging modalities. In clinical practice, steatosis is commonly detected through noninvasive imaging with ultrasonography (US), computerized axial tomography (CT) and magnetic resonance imaging (MRI) when it exceeds 25% to 30% of liver weight. Liver imaging techniques are not sensitive for the detection of many individuals with lesser degrees of

steatosis. The expense of various imaging modalities is not trivial, and none of these can distinguish simple steatosis from NASH or "uncomplicated" NASH from NASH with fibrosis. Of these, sonography is the least expensive, and MRI is the most expensive modality.⁸

On ultrasound, steatosis produces a diffuse increase in echogenicity relative to the kidneys. Fibrosis/cirrhosis has a similar appearance regardless of etiology.

On CT, steatosis produces a low-density hepatic parenchyma, which is diffuse in most people who have NAFLD. CT, as well as MR imaging, can semi-quantitatively estimate liver fat content. An unenhanced hepatic CT scan remains the optimal CT method for detection of a fatty liver. In those with a fatty liver, the hepatic attenuation is less than that of the blood vessels giving the appearance of a contrast-enhanced scan when no contrast is used.

Differences in the precession frequency between water and fat protons can be used to diagnose fatty liver using MRI. T1-weighted gradient-echo images obtained by keeping the water and fat spins out of phase show a loss of liver hepatic signal intensity relative to in-phase images. The fatty liver also has a lower signal intensity compared with adjacent muscle. Several newer modifications in MRI techniques have resulted in considerable improvement in the ability to diagnose a fatty liver by MRI.

Occasionally, fatty infiltration is focal. As a consequence, ultrasound and CT scans may be misinterpreted as reflecting malignant liver masses. MRI can distinguish space-occupying lesions from focal fatty infiltration (isolated areas of fat infiltration) or focal fatty sparing (isolated areas of normal liver).

Despite the utility of these imaging modalities in the diagnosis of diffuse fatty disorders of the liver, none of these modalities can distinguish between fatty liver vs steatohepatitis. Moreover, diffuse fibrosis is also associated with a hyper-echogenic ultrasound pattern and cannot be distinguished from fatty liver with accuracy by ultrasonography.

Thus, liver biopsy remains the only accurate way to diagnose steatohepatitis.

LIVER BIOPSY

In the absence of steatosis confirmed on liver imaging, NAFLD is estimated practically as the percentage of fat-laden hepatocytes observed by light microscopy. The spectrum of histologic abnormalities defined by NAFLD includes simple steatosis (steatosis without other liver injury) and NASH as its more extreme form. Liver biopsy is required to secure a diagnosis of NAFLD if imaging is not diagnostic (that is, if the percentage of hepatic steatosis is less than 25%–35%), and to confirm the diagnosis of NASH, fibrosis, and/or cirrhosis. In clinical practice, taking the risk of liver biopsy is often unnecessary if clinical and imaging evidence of advanced liver disease complicated by cirrhosis and portal hypertension are identified.

The value of a liver biopsy for the diagnosis of NAFLD in routine clinical practice is hotly debated. Arguments against a liver biopsy include the generally good prognosis of most patients with NAFLD, the lack of an established form of effective therapy, and the risks and costs associated with a biopsy.

Stephen H. Caldwell, MD, coauthor of one of the recent reviews on NAFLD,⁹ recently discussed liver biopsy in NAFLD.¹⁰ Lack of knowledge concerning an individual patient's extent of the disease may lead to unexplained fluid retention, inappropriate assignment of blame for liver disease to common drugs like diabetes medications, and to ill-advised dietary recommendations. Patients with fibrosis and cirrhosis may be at increased risk for adverse reactions to drugs prescribed for conditions that often coexist with NASH. Most patients with type 2 diabetes are taking ACE inhibitors because the drugs have been shown to preserve renal function. But if they have bridging fibrosis or cirrhosis on liver biopsy, the increased risk of fluid retention and ascites require consideration. It may not be advisable to stop these medications immediately, but if these problems develop, a secure

diagnosis of liver fibrosis/cirrhosis can help guide decisions regarding continuation of treatment.

A strategy that includes an observation period of up to 6 months after NAFLD/NASH is suspected is suggested. If signs and symptoms persist despite appropriate lifestyle and dietary changes, a liver biopsy can be considered.

On the other hand, there is little controversy that a liver biopsy is the only accurate method for the diagnosis of NASH, as shown by the poor positive predictive value of clinical and laboratory evaluation for the diagnosis of NASH using histology as the gold standard.

Some factors may help to identify patients with NAFLD in whom liver biopsy may provide the most prognostic information.^{11,12} An age of 45 years or more, the presence of obesity or type 2 diabetes mellitus, and a ratio of AST:ALT of 1 or greater increase the likelihood of the presence of advanced fibrosis. In the subgroup of overweight patients with a body mass index over 25, older age, higher body-mass index, and higher levels of ALT and triglycerides are also indicators of more advanced fibrosis. 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 ALT level correlate strongly with the presence of steatohepatitis; whereas hypertension and raised levels of ALT and C-peptide suggest the presence of advanced fibrosis. All of these predictor factors have not been studied adequately as predictors of progression over time. Instead, they indicate the likelihood of finding more advanced disease on the initial biopsy.

Sorbi et al¹³ recently studied the clinical utility of a liver biopsy in routine clinical practice. A total of 36 subjects with persistently elevated ALT levels for which a diagnosis could not be established by noninvasive methods underwent a liver biopsy. A presumptive diagnosis and plan of management were identified before the biopsies were performed. The liver biopsy changed the diag-

nosis in 14% of cases, as well as altered the frequency of monitoring laboratory studies in 36% of cases and the treatment recommendations in 12 patients.

Although it is essential to include only biopsy-proven cases of NASH in clinical trials, the decision to perform a liver biopsy in routine clinical practice should take into consideration the specific clinical questions that are relevant in a given case (eg, exclusion of alternate causes of liver disease, ascertainment of degree of fibrosis, and determination of long-term prognosis). Thus, both the decision to perform a liver biopsy in a patient with suspected NAFLD and the timing of the biopsy must be individualized and should include the patient in the decision-making process.

NAFLD AND THE INSULIN RESISTANCE SYNDROME

Recent studies confirm the common (although not invariable) association of NAFLD with both the metabolic syndrome X (insulin resistance syndrome) and alterations in central stress response systems. Management and treatment of NAFLD/NASH, metabolic syndrome, and the adverse effects of harmful stress response are evolving and may share important therapeutic implications, particularly if both the patient and physician are committed to the task.

Individuals at risk for the metabolic syndrome can be identified by history, physical examination and laboratory evaluation (Table 6). The metabolic syndrome is present in more than 20% of the US adult population and is associated with several potentially modifiable lifestyle factors.^{14,15} There is strong and increasing evidence that this syndrome is associated with the development of diabetes mellitus and an increased risk of cardiovascular disease. The identification and clinical management of this high-risk group is an important aspect of diabetes and coronary heart disease management and prevention.

Table 6. Metabolic Syndrome Criteria Third Report of the National Cholesterol Education Program Adult Treatment Panel III (ATP III)*

The ATP III clinical definition of the metabolic syndrome requires the presence of 3 or more of the following:

- 1) Abdominal obesity (waist circumference >40 inches in men and >35 inches in women)
- 2) High triglyceride level (≥ 150 mg/dL)
- 3) Low HDL cholesterol level <40 mg/dL for men and <50 mg/dL for women)
- 4) High blood pressure (systolic greater than or equal to 130 mm Hg or diastolic ≥ 85 mm Hg)
- 5) High fasting plasma glucose concentration (≥ 110 mg/dL)

* Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486–2497.

INSURANCE DILEMMA

Dr. Caldwell commented recently on “The Insurance Dilemma” of NAFLD.¹⁶ “A liver biopsy may help patients maintain affordable health insurance. When histology shows only Class 1 or 2 NAFLD, the condition is most likely stable and should not necessitate crushing rate hikes or denial of coverage. Insurance companies frequently reject the claims of these patients or raise the rates astronomically on the basis that high transaminase or aminotransferase levels signify a progressive disease. But for NAFLD (that has not progressed to NASH), that isn’t the case. It’s not right to label a whole group at increased risk when only a portion really is. We can make some useful distinctions based on biopsy. Insurers shouldn’t deny coverage to patients with Classes 1 and 2 steatosis. NASH patients present a more complicated ethical dilemma.”

TREATMENT OF NAFLD

There is no proven therapy for NAFLD. Clearly, more information about the natural history of NAFLD and the results of large, randomized prospective treatment trials for

patients with this disease are needed to guide future decisions. In the meantime, a number of reasonable treatment options are available. The leading Internet-based medical reference (www.UpToDate.com) states,¹⁷ “There is no proven effective therapy for NASH.” Attempts are made to modify potential risk factors such as obesity, hyperlipidemia, and poor diabetic control. Weight reduction should be gradual, since rapid weight loss has been associated with worsening of liver disease. Several potential treatments have been described, although none is used routinely for clinical practice, with the exception of vitamin E.

Stress Reduction and Lifestyle Modification

In accordance with the concept of “allostatic load,” it is reasonable to recommend that patients deploy a strategy to reduce the harmful effects of the “bad stress response,” at least with a strategy of diet, exercise and weight management. Other methods of stress management (eg, relaxation and breathing techniques, meditation, yoga) may also be incorporated.

Results from large, multicenter trials indicate that lifestyle modifications (eg, diet, exercise) significantly reduce the risk of developing type 2 diabetes. It is reasonable to recommend this approach for those with NAFLD, since the liver disorder is strongly associated with insulin resistance (metabolic syndrome X). However, it is not yet clear whether this strategy will prevent the development of NASH/fibrosis or help individuals who have already developed diabetes or who have histologically advanced NAFLD. Small studies have demonstrated that weight loss improves liver enzyme elevations in patients with NAFLD and may reduce the degree of steatosis. However, it is equally true that rapid, extreme weight loss, such as that induced by bariatric surgery, can accelerate hepatic decompensation in some patients with NAFLD.

For most patients, gradual weight loss is advisable, even though the most effective rate

and degree of weight loss have not been established. More information will be needed relative to application of weight loss techniques. Little is known about the relative importance of changing diet composition as opposed to general caloric restriction.

Exercise is an important component of most successful weight loss programs and physical activity enhances insulin sensitivity. Most people would benefit from more exercise; however, it is not clear whether merely increasing physical activity would provide the same benefits as dieting for patients with NAFLD.

Antioxidants

As discussed earlier, the pathogenesis of NAFLD has been hypothesized to be a 2-stage process with oxidative stress as the primary mediator of the second stage. Antioxidants, such as certain vitamins and minerals, would be expected to protect against liver injury.

In a few trials, treatment with vitamin E has been demonstrated to improve liver enzyme abnormalities in patients and in certain animal models with fatty liver disease. In clinical practice, gastroenterologists commonly recommend that patients with NAFLD take vitamin E, since it is cheap and well tolerated.

Other antioxidants, such as betaine, also appear to have some efficacy. Ruhl and Everhart¹⁸ recently evaluated the relationship of elevated serum alanine aminotransferase activity with iron and antioxidant levels in the United States. In this large, national, population-based study, the risk for apparent liver injury was associated with increased iron and decreased antioxidants, particularly carotenoids. Nutrients with antioxidant activity include vitamins E (alpha-tocopherol) and C (ascorbic acid), the carotenoids, and the element selenium, an essential component of the antioxidant enzyme, glutathione peroxidase. The carotenoids are a large family of compounds, the most common of which are alpha

and beta-carotene, beta cryptoxanthin, lycopene, lutein, and zeaxanthin.

Insulin-Sensitizing Drugs

Mouse models of insulin resistance and fatty liver disease have shown that treatment with metformin or thiazolidinediones improves both conditions. However, there has been some hesitancy about recommending either drug as a general therapy for NAFLD because of potential treatment-related toxicity. Troglitazone was withdrawn as a first-line therapy for type 2 diabetes because of rare, but potentially fatal, hepatotoxicity. Phenformin, the parent compound of metformin, is known to cause life-threatening lactic acidosis; thus metformin is contraindicated in patients with liver disease. Regardless, results of the same diabetes prevention trial that demonstrated the efficacy of lifestyle modifications also indicated that metformin was well tolerated in that large population of obese, insulin-resistant subjects and significantly decreased the incidence of overt diabetes. The safety and efficacy of troglitazone could not be evaluated, because that arm of the study was terminated prematurely because of concerns about potential hepatotoxicity. It remains plausible that second-generation thiazolidinediones, which appear to have less intrinsic hepatotoxicity, might be beneficial in treating NAFLD. Leptin might also have some role as a therapy for selected patients with NAFLD. In lipodystrophic mice that develop leptin deficiency caused by lipodystrophy, associated insulin-resistance and hepatic steatosis have been cured with leptin therapy, suggesting that leptin might be helpful for lipodystrophic patients with NAFLD.

Ursodeoxycholic Acid

A small study demonstrated that ursodeoxycholic acid improves liver enzyme abnormalities in NAFLD. Although data supporting its efficacy in NAFLD is sparse, hepatologists are very familiar with this drug, which is commonly used to treat cholestatic

liver diseases, and it has become a popular therapy for NAFLD. The mechanism for the putative beneficial effect of ursodeoxycholic acid in NAFLD is uncertain, and the results of at least one large ongoing trial should clarify whether or not more extensive scrutiny of this agent is justified.

Lipid-lowering Drugs

It is reasonable to consider lipid-lowering drugs as potential treatments for NAFLD, because it is a disorder of hepatic lipid homeostasis. Hypertriglyceridemia and reduced HDL cholesterol level are the types of dyslipidemia associated with NAFLD. A small trial of gemfibrozil demonstrated no appreciable effect on NAFLD. The rationale for using agents that generally lower cholesterol as therapy for NAFLD is unclear, and these agents have been associated with some incidences of liver injury. Nevertheless, a preliminary report of promising effects of atorvastatin in a small group of patients with NAFLD suggests that 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors may play some role in the treatment of this disease. However, currently, the routine use of statins to treat NAFLD cannot be recommended.

THE FUTURE

The National Institutes of Health is assembling a multicenter network to conduct large natural history and treatment trials for patients with NAFLD, while basic scientific research continues to be focused upon pathogenesis. It may soon be possible to counsel individuals about their risk for NAFLD, based upon both genetic and environmental factors. Both "nature" (ie, genetic control of inflammatory responses) and "nurture" (ie, epigenetic causes of oxidative stress and inflammation) contribute to this NAFLD. Thus, individuals who have inherited the "bad" tendency to have sustained inflammatory responses might be better off minimizing the consumption of alcohol or foods that stimu-

late cellular oxidant production and trigger inflammation or taking medications to improve their antioxidant/anti-inflammatory defenses, whereas others with "good" inflammation-control genes can be reassured that they can safely enjoy these pleasures.

The research agenda for the future includes establishing the role of insulin resistance and abnormal lipoprotein metabolism in NASH, determining the pathogenesis of cellular injury, defining predisposing genetic abnormalities, identifying better noninvasive predictors of disease and defining effective therapy.

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