

Nonalcoholic Steatohepatitis

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The association of macrovesicular steatosis of the liver with inflammation and fibrosis in people who do not consume alcohol was recognized when liver failure followed jejunoileal bypass surgery for morbid obesity. The hepatic histological characteristics were indistinguishable from those seen in alcoholic hepatitis. Subsequently, similar hepatic histological characteristics were reported in obese women, especially those with diabetes, who neither abused alcohol nor had undergone bariatric surgery. The term nonalcoholic steatohepatitis (NASH) was introduced to describe this syndrome. The clinical spectrum of the disease has been expanded by its occurrence in nonobese subjects and males. This condition has also been referred to as nonalcoholic steatonecrosis, fatty liver hepatitis, and non alcoholic fatty hepatitis.

SPECTRUM OF LESIONS SEEN IN NONALCOHOLIC FATTY LIVER DISEASE

- **Macrovesicular fatty liver**
- **Steatohepatitis**
- **Steatohepatitis with fibrosis**
- **Cirrhosis**

Table 1

Histological Spectrum

Macrovesicular fatty disorders of the liver encompass a spectrum of histological lesions (Table 1), including fatty liver alone at one end of the spectrum and advanced cirrhosis at the other. The fat is distributed as a large cytoplasmic globule with displacement of the nucleus to the edge of the cell. The steatohepatitis lesion is also defined by the additional presence of

Mallory bodies ballooning degeneration, predominantly lobular inflammation, or perisinusoidal fibrosis (Table 2). In most instances, only some of these findings are present, and the diagnosis often rests on the overall gestalt of the pathologist.

Macrovesicular steatosis is also seen in some patients with atypical features of NASH, such as predominantly portal inflammation, rare or absent Mallory bodies and no fibrosis. Whether these patterns of hepatic histological features in a person who does not abuse alcohol represent a variant of NASH or other distinct entities is controversial.

Many other disorders, including hepatitis C, are associated with hepatic inflammation and macrovesicular fatty change. Although these are examples of steatohepatitis, the term is usually reserved only for the previously noted constellation of histological findings (Table 2). Only a subset of people with fatty liver have steatosis and inflammation, and even few have steatohepatitis.

Although the histological severity of NASH represents the activity of the steatohepatic lesion, no universally accepted grading system has been appropriately validated. Ballooning degeneration, Mallory hyaline, and inflammatory activity are factors that determine severity. The histological stage of disease may indicate how far it has progressed toward cirrhosis by the degree of fibrosis present. Bridging fibrosis represents an advanced stage of NASH, and patients with this finding may progress more steadily to cirrhosis and liver failure.

Etiologic Associations

NASH may represent the hepatic component of a metabolic syndrome characterized by obesity, hyperinsulinemia, peripheral insulin resistance, diabetes, hypertriglyceridemia, and hypertension (Table 3). Although the molecular basis of these interactions is unclear, their clinical association is well established.

Although obesity, which is defined by a body mass index $>30 \text{ kg/m}^2$, is clearly associated with NASH, most patients are only moderately overweight, at 10%-40% greater than their ideal body weight. The likelihood of developing NASH increases with the degree of obesity, and 15%-20% of morbidly obese patients have this condition. Those with truncal obesity are more prone to develop diabetes, as well as a fatty liver. However, obesity is not invariably present, and many individuals with NASH have a normal body weight.

Non-insulin-dependent diabetes mellitus is a major component of the metabolic syndrome and is associated with obesity, as well as NASH. Both obesity and non-insulin-dependent diabetes mellitus are associated with peripheral insulin resistance, hyperinsulinemia, increased levels of free fatty acids (FFAs), and hypertriglyceridemia. The lipid and endocrine metabolic abnormalities common to these conditions have an important role in the genesis of NASH.

A histological picture of steatohepatitis has also been associated with several drugs, such as diltiazem, amlodipine, and tamoxifen; the rare lipid metabolic disorders of abeta

HISTOLOGICAL FINDINGS IN STEATOHEPATITIS

- **Macrovesicular steatosis**
- **Mallory Bodies**
- **Ballooning degeneration**
- **Perisinusoidal fibrosis (mainly pericentral)**
- **Scattered, predominantly lobular, neutrophilic, or mixed inflammation**

lipoproteinemia; and syndromes of insulin resistance, such as lipodystrophic diabetes and Mauriac syndrome (Table 3). Even occupational exposure to several types of solvents has been reported with steatohepatitis. Steatohepatitis in these populations is best considered separately from the commonly seen NASH.

Nomenclature

The term using the prefix "nonalcoholic" with the histological lesion of steatohepatitis is associated with numerous causes (*Table 3*). Calling the lesion in all these conditions NASH implies that its underlying mechanism and natural history are identical regardless of the etiologic association, but this remains to be proven.

An optimal way to diagnose or classify fatty liver disorders may use a two-part nomenclature system: (1) a description of the histological characteristics, such as steatosis or steatohepatitis; for example, steroid-induced fatty liver in a patient with autoimmune hepatitis or steatohepatitis;

CONDITIONS ASSOCIATED WITH STEATOHEPATITIS

- Syndrome X
- Obesity
- Diabetes mellitus
- Hypertriglyceridemia
- Hypertension
- Lipid disorders
- Abetalipoproteinemia
- Hypobetalipoproteinemia
- pharmaceuticals
 - Amiodarone
 - Diltiazem
 - Tamoxifen
- Lipoatrophy
- Total parenteral nutrition
- After jejunioileal bypass for morbid obesity
- Occupational exposure to solvents

Table 3

and (2) a descriptor of the etiologic association, as in alcohol, total parenteral nutrition, drugs, or lipid disorders. The term NASH would then apply to those without etiologic associations or with diabetes or obesity as the only associations.

Pathogenesis

A popular, although not fully understood, model of pathogenesis is the two-hit hypothesis (1) increased delivery of FFAs to the liver, and (2) the consequences of these FFAs to the liver. NASH is associated with insulin resistance and increased peripheral lipolysis, which makes more FFAs available for uptake by the liver. Such insulin resistance is present even in those without diabetes.

The consequences of increased fatty acid uptake by hepatocytes include increased mitochondrial beta oxidation, peroxisomal fatty acid oxidation, and re-esterification to form triglycerides. These processes increase free radical generation in hepatocytes, causing membrane lipid peroxidation, hepatocyte injury; and cell death. Increased iron stores, as well as activation of the cytochrome P450 system, are other factors implicated in hepatocyte injury. Activation of hepatic stellate cell by-products of hepatocyte injury produces hepatic fibrosis.

Epidemiology

Incidence and Prevalence

The true incidence and prevalence of NASH are unknown because liver biopsy is required to establish the diagnosis. Virtually all published studies in a hospital setting use liver biopsies in highly selected patient groups. In contrast, large population based studies have used laboratory and clinical profiles along with imaging along with imaging modalities, which are inadequate to distinguish between fatty liver alone, cryptogenic hepatitis, and NASH.

An important, unselected autopsy study of apparently nonalcoholic subjects found steatohepatitis in 3% of lean individuals and 19% of obese patients. Additional risk factors included diabetes, rapid preterminal weight loss, and the use of intravenous dextrose in the last week of life.

DEMOGRAPHICS

AUTHOR	NO. OF PATIENTS	MEAN AGE (Y)	WOMEN (%)	1	OBESE (%)
Ludwig	20	54	65		90
Diehl	39	52	81		81
Lee	49	53	78		78
Laurin	40	48	72		70
Bacon	33	47	42		39
Teli	40	57	45		30
George	51	47	49		?

Table 4

Several facts stand out consistently: (1) Fatty liver, as well as NASH, occurs in all age groups. (2) The prevalence increases with increasing body weight because fatty liver has been documented in up to 15% of normal individuals and 80% of the morbidly obese. (3) Correspondingly, -3% of non-obese and 15%-20% of morbidly obese subjects have steatohepatitis.

Demographics

NASH has been reported in all age groups older than 10 years, with the greatest prevalence in those aged 40-49 years. Although studies published before 1990

SYMPTOMS

	PREVALENCE
Asymptomatic	17/62
Fatigue	45/62
Right upper quadrant discomfort	30/62
Edema	6/62
Pruritus	4/62
Gastrointestinal bleeding	2/62
Ascites	2/62

Table 5

SIGNS

	PREVALENCE
Normal examination	12/62
Hepatomegaly	45/62
Stigmata of liver disease	10/62
Edema	6/62,
Jaundice	3/62
Splenomegaly	2/62
Ascites	2/62

Table 6

(Table 4) emphasized that NASH occurred mostly in women, recently it has been found frequently in men. The fibrotic component of NASH appears to be more prominent in Japanese subjects in a manner analogous to alcoholic liver injury.

Familial Occurrence

Obesity and diabetes are often clustered within families because of both genetic and environmental factors. However, results of such a familial incidence of NASH are rare. Fatty liver has been described in patients with hypobetalipoproteinemia, but despite the presence of an underlying familial disorder, the prevalence of fatty liver or steatohepatitis in the affected families has not been systematically studied. Three members of a family have been reported with diabetes, fatty liver, and a hemolytic anemia because of high levels of red-cell Mg²⁺-adenosine triphosphatase.

Clinical Spectrum

Symptoms

Most patients with NASH are asymptomatic, and the liver disease is either discovered incidentally during laboratory examination or during evaluation of hypertension, diabetes, or morbid obesity (Table 5). Because gallstones are more prevalent in obese individuals, sonographically diagnosed fatty liver has been associated with an increased prevalence of gallstone disease.

Fatigue is probably the most commonly reported symptom of NASH, but it does not correlate well with the severity of the histological lesion. Right upper quadrant discomfort, although common, is often reported after the patient is made aware of the presence of a liver ailment.

Few patients experience symptoms indicative of more serious liver disease and may develop pruritus, anorexia, and nausea. Symptoms of decompensated cirrhosis can occur with jaundice, indicating advanced liver disease.

Signs

No signs of NASH are pathognomonic. Obesity is common (Table 6), and hepatomegaly has been reported in up to 50% of the subjects. A lesser number have stigmata of chronic liver disease, such as spider nevi and palmar erythema. Jaundice, asterixis, and fluid retention occur in those with advanced cirrhosis. Muscle wasting is often underestimated because of edema and pre-existing obesity.

Test Result Abnormalities

Most patients with NASH have abnormal transaminase levels (Table 7), but the degree of enzyme level elevation is not marked and is usually one to four times the upper limits of normal. The alanine aminotransferase (ALT) level is usually greater than the aspartate aminotransferase (AST) level, but a greater AST level may indicate the presence of cirrhosis. The AST/ALT ratio is almost never greater than 2. Infrequently, the serum ALT level remains persistently normal. Alkaline phosphatase level may also be elevated up to twice the upper limits of normal.

As expected, hepatic synthetic functions remain intact until advanced cirrhosis develops. In a patient with diabetes with NASH, isolated hypoalbuminemia may be caused by proteinuria related to diabetic nephropathy. Hematologic parameters are normal unless cirrhosis and portal hypertension lead to hypersplenism. Up to 25% of the patients may have positive results for antinuclear anti-body or other markers of autoimmune disease, but the significance of this observation is unclear.

Almost half the patients with NASH are either frankly diabetic or have postprandial blood glucose levels >200 mg/dL. A fasting lipid profile shows hypertriglyceridemia in 20%-80% of the patients, whereas hypercholesterolemia occurs less often.

Markers of Iron Overload

Biochemical evidence of iron overload (increased serum ferritin level and transferrin saturation) is present in 25%-50% of the patients with NASH. However, The hepatic iron index is almost always <1.9, the diagnostic cutoff for hemochromatosis. A recent study found 31% of the patients were either homozygous or heterozygous for the Cys282Tyr mutation, a figure significantly greater than that in the general population. In contrast, the prevalence of the His63Asp mutation was no greater than expected. When iron overload is present, the rate of progression of fibrosis in patients with NASH is accelerated.

Diagnosis

Three criteria have been proposed for the diagnosis of NASH (*Table 8*):
(1) a histological picture of steatohepatitis, (2) convincing evidence of minimal or no alcohol consumption

TEST RESULT ABNORMALITIES IN NASH

PARAMETER	DEGREE/PREVALENCE QF ABNORMALITY
<i>Markers of liver injury</i>	
AST	Usually up to 4-5 fold elevation
ALT	Usually up to 4-5 fold elevation
Alkaline phosphatase	Usually up to 2-fold elevation
AST/ALT Ratio	<1 in most cases
<i>Markers of liver failure</i>	
Bilirubin	Elevated in late stages of disease
Albumin	Decreased in late stages of disease
Prothrombin time	Prolonged in late stages of disease
Serum markers of iron overload	25%-50% of subjects
Hepatic iron index	Almost always <1 .9
Antinuclear antibody	15%-20% of sub₁jects (usually low titer)

(<+0 g/wk), and (3) absence of serological evidence of viral hepatitis. However, each of the criteria has limitations.

The histological criteria for the diagnosis of steatohepatitis include macrovesicular steatosis; evidence of ballooning degenerations; Mallory bodies; scattered, predominantly lobular, inflammatory infiltrate; and perisinusoidal fibrosis. Many histological variants of this classic picture have been ascribed with controversy to NASH.

Determining the extent of alcohol consumption is no easy task. Patient reports are notoriously inaccurate and interrogating family members may be useful. Direct and surrogate markers of alcohol consumption include random blood alcohol examinations, serum γ -glutamyl transferase levels, mean corpuscular volume, AST levels, AST/ALT ratio, mitochondrial AST, and desialylated transferrin. Unfortunately, none of these are sensitive or specific enough to be valuable clinically. Recently, the ratio of desialylated versus total transferrin and plasma pseudocholinesterase has been proposed as a marker of alcoholism. Its clinical use remains to be established.

The presence of non-A, non-B hepatitis (hepatitis C) was originally believed to constitute an exclusion criterion for the diagnosis of NASH. However, there are patients with hepatitis C who clearly have histological evidence of a classic

steatohepatitis rather than the predominantly portal lymphocytic infiltrate with the mild-to-moderate steatosis seen in hepatitis C. In such cases, the presence of two diagnoses, hepatitis C and NASH may be considered.

DIAGNOSTIC CRITERIA FOR NASH

Histological picture of steatohepatitis

Convincing evidence of minimal or no alcohol consumption (<40 g/wk)

Absence of serological evidence of viral hepatitis

Table 8

Noninvasive Studies

No accurate noninvasive methods can diagnose NASH because the presence, degree, and pattern of transaminase level elevation are nonspecific and do not provide a specific diagnosis. Even when the index of suspicion in an obese individual with diabetes is high, transaminase levels do not distinguish between fatty liver alone versus NASH. Various imaging modalities can diagnose the presence of a diffuse fatty liver.

Sonography is the least expensive radiologic method to detect a fatty liver. There are four sonographic findings of diffuse fatty change in the liver: (1) diffuse hyperechoic echo texture (bright liver), (2) increased liver echo texture compared with the kidneys, (3) vascular blurring, and (4) deep attenuation. A small retrospective study combined these parameters to diagnose fatty liver (defined histologically by fat present in >30% of each lobule) with a sensitivity of 83% and specificity of 100%.

Liver fat content can be semi quantitatively estimated by computed tomographic scan. Normally, the computed tomographic attenuation values for the liver range from 50-75 Hounsfield units (HU). With increasing hepatic steatosis, the liver attenuation values decrease by -1.6 HU for every milligram of triglyceride deposited per gram of liver tissue. Thus, 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 even when contrast is not used. If intravenous contrast is used, both the liver and splenic attenuation values increase. However, the hepatic values increase to a lesser degree than splenic values, thereby increasing the difference in hepatic to splenic values. In such films, a difference of 18-20 HU is considered diagnostic of fatty liver. If hepatic attenuation is greater than that of the spleen, fatty liver can be excluded. Conventional magnetic resonance imaging methods are not very useful for the diagnosis of fatty liver.

Most of these imaging modalities can distinguish between fatty liver and NASH. Moreover, diffuse fibrosis is also associated with a hyperechogenic ultrasound pattern. Liver biopsy remains the only accurate way to diagnose NASH.

Role of Liver Biopsy

The need for a liver biopsy to diagnose NASH in routine clinical practice is debatable. Arguments against a liver biopsy include the generally good prognosis of most patients with NASH, lack of an established form of effective therapy, and risks and costs associated with biopsy. A liver biopsy should be performed to answer specific clinical questions, such as the exclusion of cryptogenic hepatitis, ascertainment of degree of fibrosis, and determination of long-term prognosis. Diagnosis of fatty liver alone may facilitate an individual obtaining life insurance.

Alcoholic Steatohepatitis Versus NASH

In hospitalized populations, those with alcoholic hepatitis are sicker than those with NASH and have a greater serum bilirubin level and an AST/ALT ratio >2. The AST/ALT ratio is less useful in an ambulatory setting. The pathological changes of alcoholic steatohepatitis are more severe, with greater inflammation, greater degree of hepatocellular injury, frequent Mallory bodies, and greater degree of perisinusoidal fibrosis. Those with nonalcoholic liver disease have a greater prevalence of glycogenated nuclei. Whereas only 8%-10% of the patients with NASH have cirrhosis, 39% of ambulatory patients and 80%-90% of hospitalized patients with alcoholic hepatitis also have cirrhosis. These data indicate that distinction between NASH and alcoholic steatohepatitis may not always be easy, especially in those who consume moderate amounts of alcohol. In such individuals, reassessment only after a period of abstinence may establish the diagnosis of NASH.

Natural History of Nonalcoholic Fatty Liver Disease

There are several distinct histological stages in the natural history of nonalcoholic fatty liver disorders. These include a fatty liver alone, steatohepatitis, steatohepatitis with fibrosis, and eventually cirrhosis. After the development of cirrhosis, fatty change may disappear. Many patients with cryptogenic cirrhosis may have originally had NASH that progressed to cirrhosis.

The majority of subjects with nonalcoholic fatty liver have a fatty liver alone. Such patients rarely progress to steatohepatitis or steatosis with fibrosis. However, morbidly obese individuals with a fatty liver alone frequently develop steatohepatitis after rapid weight loss following jejunioileal bypass or proximal gastric bypass.

At initial presentation, up to 40% of the patients with NASH have advanced fibrosis, whereas 10%-15% have established cirrhosis. One study found that patients with cirrhosis were more likely to be women (62%) and obese (62%), but another study did not find a relationship between histological stage and presence or degree of obesity or diabetes. In contrast, 40%-50% of the patients with alcoholic steatohepatitis become cirrhotic. No clinical features predict progression to cirrhosis, but the presence of fibrosis and iron overload on initial biopsy are histological risk factors for the development of cirrhosis.

Recent reports have challenged the notion that NASH is associated with a low (<5%) mortality rate. Study of 30 patients with NASH followed up for >10 years found the overall mortality was not significantly different from that of an age and sex-matched population, but the liver-related mortality increased. Patients with bridging fibrosis or cirrhosis are at greater risk for death as a consequence of NASH.

Many factors contribute to mortality in patients with NASH. These include obesity, diabetes, and its complications; other comorbidities associated with obesity and diabetes; and the liver disease itself, with the development of liver failure, complications of cirrhosis, and hepatocellular carcinoma. Liver failure often manifests during period of rapid weight loss regardless of its mechanism. After weight loss, the liver histological state often improves, with decrease in inflammation, number of Mallory bodies, and even perisinusoidal fibrosis, particularly when weight loss is achieved slowly and exercise is a part of the weight-loss regimen.

NASH In Selected Patient Populations

Children

In a retrospective review of liver biopsies performed in children, 12% had steatohepatitis, but only 2% were considered to have NASH. Other studies found 50%-90% of obese children had sonographic evidence of fatty liver. Because 25%-30% of the children in the age group of ~12 years and 70%-100% of the children in the age group of 12-17 years are obese, nonalcoholic fatty liver disease is probably common in the general population.

The clinical picture of NASH in the pediatric population is similar to that in adults. Right upper quadrant aching and fatigue are the most commonly reported symptoms. Obesity and hepatomegaly are the most commonly seen physical findings. Affected children usually have an elevated ALT level, but unlike adults, cirrhosis from NASH has not been reported.

The Morbidly Obese Individual

The recognition of NASH as a clinical entity has its origin in descriptions of fatty liver and fibrosis, along with various degrees of inflammation in morbidly obese individuals. In a comprehensive review, fatty change was present in 75% of morbidly obese patients, whereas partial inflammation and fibrosis occurred in ~25% and cirrhosis in 3% of the individuals. No relationship between the extent of liver injury and degree of obesity, age, sex, or presence of diabetes has been found.

A characteristic feature of morbid obesity-related steatohepatitis is subacute hepatic failure leading to death after rapid, marked weight loss, usually because of jejunoileal bypass. Preoperative perisinusoidal fibrosis is a risk factor for the postoperative development. Some, but not all, patients respond to reversing the shunt.

This danger of jejunoileal bypass has led to development of proximal gastric bypass as a safer procedure for bariatric surgery. However, the risks for worsening liver histological state are linked to the rapidity of weight loss rather than the type of surgery. Liver histological characteristics studied before and after gastroplasty in morbidly obese subjects found the degree of steatosis improved after weight loss. However, this was associated with an increase in lobular inflammation. Although the risks for subacute liver failure are less after gastroplasty, the long-term clinical significance of this change in liver histological state remains unclear.

Liver Transplantation

Fatty disorders of the liver affect the availability of organs, as well as the outcomes of orthotopic liver transplantation (OLT). Recent data indicate that up to 20% of potential donors have hepatic steatosis, which precludes the use of such livers for transplantation. Potential mechanisms that contribute to poorer function of the fatty grafts include decreased ability to generate adenosine triphosphate and the generation of toxic metabolites. The high prevalence of fatty change in potential organ donors may reflect both the high prevalence in the population and the use of dextrose solutions before the declaration of brain death.

Although up to 12% of all cases of cirrhosis may be related to NASH, only a few studies document patients with NASH who have undergone OLT. Some patients with cirrhosis who have undergone OLT probably had NASH. Patients with

TREATMENTS

Modalities that decrease fat delivery to the liver

- Gradual, medically supervised weight loss
- Control of diabetes
- Drugs to improve insulin resistance (such as metformin)

Modalities that protect hepatocytes from oxidative stress

- Vitamin E
- UDCA
- lecithin
- Selenium
- Betaine

- None of these treatments have been conclusively shown to improve NASH.

Table 9

NASH do well after OLT, at least in The short term. However, NASH can recur, and some patients develop fibrosis relatively soon. In those with prior morbid obesity and liver failure precipitated by a jejunoileal bypass, severe NASH with fibrosis has been reported after OLT, necessitating reversal of the bypass. Although obesity frequently occurs along with hypertriglyceridemia after OLT, the *de novo* development of NASH is distinctly rare.

Treatment Of NASH

No therapy has clearly proved effective for the treatment of NASH. Treatment has therefore been directed toward the correction of the risk factors for NASH, decreasing the delivery of fatty acids to the liver, and use of drugs with potentially hepatoprotective effects (*Table 9*).

Weight Loss, Exercise, and Control of Diabetes

Obesity and diabetes are important risk factors for the development of both fatty liver and NASH. After weight loss, the histological findings of NASH improve, especially when weight loss is gradual and exercise is an important component of the weight-loss program. Both weight loss and exercise improve insulin resistance, which appears to have an important role in the genesis of NASH. Obese subjects with NASH need a supervised weight-loss program. Rapid weight loss should be avoided because of the risk for precipitating severe steatohepatitis and liver failure. Those with normal body weights should be encouraged to lead an active lifestyle. Diabetes should be controlled with appropriate agents.

Morbidly obese subjects considered for more aggressive weight-loss programs, including proximal gastric bypass, should be carefully evaluated for the presence of other obesity-related diseases. The risk for developing decompensated liver disease during rapid weight loss must be integrated with the clinical profile of the patient to develop an individually tailored treatment plan.

Lipid-Lowering Agents

Hypertriglyceridemia is often associated with NASH. In one controlled trial, clofibrate did not benefit liver function test results or hepatic histological state. In another gemfibrozil improved liver chemistry test results, but no histological data were available. The use of such agents for the treatment of NASH is still open to question.

Reduction of Insulin Resistance

Abnormal liver enzyme levels in patients with NASH improve after treatment with metformin and troglitazone, drugs that reduce insulin resistance. Troglitazone has been associated with severe hepatotoxicity. Because those with pre-existing liver disease are more likely to develop severe liver failure if hepatotoxicity occurs, troglitazone should be avoided. The value in NASH of rosiglitazone and pioglitazone, second-generation drugs without reported hepatotoxicity, remains to be established.

Drugs That Protect Hepatocytes

Drugs believed to be hepatoprotective include ursodeoxycholic acid (UDCA), vitamin E, lecithin, betacarotene, and selenium. Of these, the first two have been most studied in patients with NASH. Vitamin E administration in children with steatohepatitis led to normalization of liver enzyme levels after several months of therapy. Although no data exist on the effects of vitamin E on liver histological characteristics, it is frequently used to treat NASH.

The value of UDCA, a hydrophilic bile acid with hepatoprotective properties, on NASH was examined in a controlled trial and was shown to improve liver enzyme levels and cause a decrease in hepatic steatosis. Although the long-term effects of UDCA, as well as its optimal dose, are not yet established, it is often used for the treatment of NASH because of its minimal adverse effect profile and the evidence for short-term efficacy. The usual dose of UDCA is 10-15 mg/kg/d orally.

Reduction in Hepatic Iron Content

The presence of iron overload is associated with accelerated hepatic fibrosis in patients with NASH. Those found to have excess iron by both biochemical markers and histological examination may be considered for phlebotomy until they become marginally iron deficient.

Summary

Nonalcoholic fatty disorders of the liver represent a spectrum of conditions with macrovesicular fatty

change in the liver. They are commonly, but not always, associated with obesity and diabetes. Those without hepatic fibrosis have an excellent prognosis for at least 10 years. However, with advanced fibrosis or cirrhosis, patients with this condition are at increased risk for liver-related mortality. Rapid weight loss can precipitate severe NASH, whereas gradual weight loss and exercise are beneficial. Treatment is directed at underlying diseases and may include the use of UDCA or vitamin E. In those with iron overload, phlebotomy may be considered.

Recommended Readings

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