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AGA Technical Review on Nonalcoholic Fatty Liver Disease

This literature review and the recommendations therein were prepared for the American Gastroenterological Association (AGA) Clinical Practice Committee and the American Association for the Study of Liver Diseases (AASLD) Practice Guidelines Committee. The paper was approved by the Clinical Practice Committee on March 3, 2002, and by the AGA Governing Board on May 19, 2002. It was approved by the AASLD Governing Board and AASLD Practice Guidelines Committee on May 24, 2002.

Nonalcoholic fatty liver disease (NAFLD) represents a spectrum of conditions characterized histologically by mainly macrovesicular hepatic steatosis and occurs in those who do not consume alcohol in amounts generally considered to be harmful to the liver. There are 2 histologic patterns of NAFLD: fatty liver alone and steatohepatitis. NAFLD is an increasingly recognized cause of liver-related morbidity and mortality. In this review, the existing literature regarding the nomenclature, clinical and histologic spectrum, natural history, diagnosis, and management of this condition are discussed.

Methods

This report is based on the following: (1) a formal review and analysis of the literature on NAFLD (*Index Medicus*, 1950–1966; MEDLINE, 1966–2001), (2) several published guidelines and meta-analyses, including the American Gastroenterological Association's policy statement on guidelines, (3) the Manual for Guideline Development (American Gastroenterological Association: Clinical Practice and Practice Economics Committee)[1] as well as the policy statement on the development and use of practice guidelines of the American Association for the Study of Liver Diseases,[2] and (4) 12 years of experience on the part of the author in managing patients with liver diseases. There is a paucity of controlled data (types I and II as defined by the NHS center for reviews and dissemination)[3] on NAFLD. This report summarizes the published literature and includes reported case series and case reports. Letters and abstracts have been included only when they represent the only literature in a given area or have been cited frequently in existing literature.

History of Discovery of NAFLD

The association of macrovesicular steatosis of the liver with inflammatory changes and fibrosis in obese subjects has been known for several decades.[4] However, it was largely ignored as a clinical entity until several reports[5–7] documented the development of liver failure in some patients following surgical jejunoileal bypass for morbid obesity. The hepatic histology in such patients was indistinguishable from that seen in alcoholic hepatitis and included macrovesicular steatosis, Mallory bodies, ballooning degeneration, hepatocyte necrosis, and fibrosis.[8] Similar hepatic lesions subsequently were described in obese patients who had neither abused alcohol nor undergone weight-loss surgery[9–11] and in diabetic individuals.[12–14] In 1980, Ludwig et al.[15] introduced the term "nonalcoholic steatohepatitis" (NASH) to describe these histologic findings in those who did not consume alcohol. Other synonyms used to describe this entity include nonalcoholic steatonecrosis,[16] fatty liver hepatitis,[9] and nonalcoholic fatty hepatitis.[17]

Nomenclature

A complete diagnosis of fatty liver disease ideally should define the histology, including the stage and grade of the disease as well as its etiology (Table 1). 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), and the underlying mechanisms as well as the natural history of the disease may vary with the specific etiology. Using the term "nonalcoholic" to describe fatty liver disease associated with all of these etiologies renders the condition heterogeneous in terms of etiology and, possibly, 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 nucleus to the edge of the cell.[18–21] The original descriptions of steatohepatitis included the additional presence of Mallory bodies, ballooning degeneration, predominantly lobular neutrophilic inflammation, and Rappaport zone III perisinusoidal fibrosis.[9,13,15,18] It is now appreciated that, in a given patient, only some of these features may be present.[22] Mallory bodies are less frequently seen in NASH

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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
- Clinical association
  1. Alcohol
  2. Insulin resistance
  3. Drugs
  4. Lipid disorders
  5. Toxic
  6. Weight loss
  7. Idiopathic

compared with alcoholic steatohepatitis and may even be absent.[23,24] Also, in many individuals, atypical features (e.g., 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 in 1998, no consensus exists on this subject.

An important consideration is the reliability with which the individual histologic parameters of steatohepatitis can be recognized. Nineteen individual parameters grouped under steatosis, hepatocyte injury, inflammation, and fibrosis were evaluated in a blinded manner by 4 pathologists and twice by 2 pathologists in one study.[25] Substantial concordance was observed with respect to assessment of extent of steatosis, sinusoidal location of steatosis, perivenular fibrosis, grade of fibrosis, ballooning degeneration, and glycogen nuclei. There was, however, considerable interobserver variation in the assessment of inflammation.

Grading and Staging of Steatohepatitis

An universally accepted histologic grading and staging system for steatohepatitis does not exist. The histologic grade indicates the activity of the steatohepatitic lesion, whereas the stage reflects the degree of fibrosis (Table 1). In a retrospective analysis,[26] those with florid steatohepatitis characterized by fat, ballooning degeneration, Mallory bodies, or perisinusoidal fibrosis had a poorer long-term outcome than those with fat and only nonspecific lobular inflammation. Based on these findings, the former histologic phenotype has been referred to as "big NASH" and the latter as "little NASH." This remains to be prospectively validated.

In another study, Brunt et al.[27] scored a total of 10 findings to develop a grading and staging system for NASH. 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 hepatic fibrosis were scored: perisinusoidal fibrosis, portal fibrosis, and bridging fibrosis. Based on these, the necroinflammatory activity was graded as mild, moderate, or severe (Table 3). It was found that the serum alanine aminotransferase (ALT) levels correlated with the severity of the grade of steatohepatitis. The stage of the disease was further classified from 1 to 4 based on the degree of fibrosis. This grading and staging system has not yet been prospectively validated.

Clinical Spectrum of NAFLD

NAFLD is a heterogeneous disorder. The heterogeneity stems from the variability in the definitions of the term "steatohepatitis" as well as its varied clinical associations. The epidemiology, clinical associations, and clinical features of NAFLD are reviewed below.

Epidemiology of NAFLD

Incidence and prevalence. The true incidence and prevalence of NAFLD are unknown. The published studies may be divided into 2 broad categories: (1) studies focused on selected patient subpopulations and (2) population-based studies. Virtually all of the former studies focus on specific subsets within a hospital-based patient population (e.g., diabetic or obese individuals),[11,28,29] thereby introducing both selection

Table 2. Conditions Associated With Steatohepatitis

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. Jejunoileal bypass
   b. Gastric bypass[a]
   c. Severe starvation
6. Iatrogenic
   a. Amiodarone
   b. Diltiazem
   c. Tamoxifen
   d. Steroids
   e. Highly active antiretroviral therapy
7. Refeeding syndrome
8. Toxic exposure
   a. Environmental
   b. Workplace

NOTE. All conditions except alcoholism are usually referred to as nonalcoholic steatohepatitis.

[a]Much less common than after jejunoileal bypass.

Table 3. Grading and Staging of NAFLD

Grading NAFLD	
1. Macrovesicular steatosis	
Grade 0: None	
Grade 1: Up to 33%	
Grade 2: 33%–66%	
Grade 3: > 66%	
2. Necroinflammatory activity	
Grade 1 (mild)	Steatosis up to 66%, occasional ballooned hepatocyte (mainly zone 3), 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 NAFLD	
1. Stage 1	Zone III perisinusoidal/pericellular fibrosis; focally or extensively present
2. Stage 2	Zone III perisinusoidal/pericellular fibrosis with focal or extensive periportal fibrosis
3. Stage 3	Zone III perisinusoidal/pericellular fibrosis and portal fibrosis with focal or extensive bridging fibrosis
4. Stage 4	Cirrhosis

Data from Brunt et al.[27]

and ascertainment bias. Population-based studies have primarily used imaging modalities to diagnose NAFLD.[30–34] Although such studies can detect a fatty liver, they do not provide data on steatohepatitis, which requires a liver biopsy for confirmation.

Fatty liver disease was found in 20% of 126 otherwise healthy young adults with normal ALT levels being evaluated as donors for adult living-related orthotopic liver transplantation (OLT).[35] These data corroborate studies of automobile and air-crash victims who underwent liver biopsies.[36] In an autopsy study of 351 apparently nonalcoholic subjects,[37] steatohepatitis was found in 2.7% of lean individuals and 18.5% of obese patients. The risk factors for steatosis included diabetes, rapid preterminal weight loss, and the use of intravenous dextrose in the last week of life. These data, however, may be potentially biased due to preterminal events that could have led to a fatty liver.

Despite the limitations of the published data, several facts stand out consistently. Fatty liver and NASH occur in all age groups.[38,39] The prevalence increases with increasing body weight,[19,31,40–43] and fatty liver has been documented in up to 10%–15% of normal individuals and 70%–80% of obese individuals. Correspondingly, about 3% of nonobese individuals[37] and 15%–20% of morbidly obese subjects[28,38] have steatohepatitis. These findings are particularly of concern given the increasing prevalence of obesity in virtually all age groups.[44–46]

Demographics. Both fatty liver and NASH have been reported in all age groups, including children.[33,47] The highest prevalence is in those between 40 and 49 years of age.[22,29,38,39,48] Although studies published before 1990[15,49,50] (Table 4) emphasized that NASH occurred mostly in women (53%–85% of all patients), more recent studies[22,29] have shown that NASH occurs with equal frequency in men (~50%). Interestingly, it has been suggested that the fibrotic component is reported to be more prominent than the inflammatory component in Japanese subjects in a manner analogous to alcoholic liver injury in these subjects.[51] Within the United States, little data on the ethnic breakdown of subjects with NAFLD are available.

Familial clustering of NAFLD. Obesity[52] and diabetes[53] are often clustered within families. The causes of such familial clustering include both genetic and environmental factors.[54] One would therefore also expect cases of steatohepatitis to be clustered within families, especially if several members are obese or diabetic. In a recent study,[55] 8 families with a total of 18 members with NAFLD, including NASH with cirrhosis, were described. A clear-cut pattern of inheritance of risk for NAFLD was not identified. However, the risk factors for NAFLD within these kindreds included female sex, obesity, and type 2 diabetes mellitus. Others have also reported the occurrence of NAFLD in multiple members of a family.[56] Several instances of fatty liver also have been described in patients with rare familial disorders (e.g., hypobetalipoproteinemia)[57,58] and a kindred with diabetes and hemolytic anemia due to a deficiency of red cell Mg^{2+}–adenosine triphosphatase.[59] In such cases, despite the presence of an underlying familial disorder, no systematic studies of the prevalence of fatty liver or steatohepatitis in the affected families have been reported.

There is increasing evidence that NAFLD often represents the hepatic component of a "metabolic" syndrome characterized by obesity, hyperinsulinemia, peripheral insulin resistance, diabetes, hypertriglyceridemia, and hypertension (Figure 1).[14,34,42,60–64] Although the molecular basis of these interactions is not fully understood and is currently the subject of intense investigation, their clinical association seems to be well established.

Obesity, defined by a body mass index (BMI) >30 kg/m^2,[65] is clearly associated with NASH. However, most patients are only moderately overweight and are 10%–40% over their ideal body weight.[37,50,66] The likelihood of developing NASH

Table 4. Histologically Characterized Series of Cases With NAFLD

Author (*yr*)	Study design	n	Follow-up	Obese (%)	Diabetes (%)	↑ Triglyceride (%)	Female (%)	Symptomatic (%)	Advanced fibrosis (%)
Hilden et al.[149] (1973)	Series (r)	32	Up to 33 yr	NA	NA	NA	NA	NA	NA
Adler and Schaffner [93] (1979)	Case series (r)	29	NA	100	2	48	76	NA	47
Ludwig et al.[15] (1980)	Case series (r)	20	NA	90	50	67	65	NA	15
Itoh et al.[101] (1987)	Comparative-case series (r)	16	NA	100	5	63	75	NA	19
Diehl et al.[49] (1988)	Comparative-case series (r)	39	NA	71	55	20	81	23	39
Lee [50] (1989)	Case series (r)	49	NA	69	51	NA	78	0	34
Powell et al.[48] (1990)	Case series (r)	42	Up to 21 yr	95	36	81	83	52	50
Bacon et al.[22] (1994)	Case series (r)	33	NA	39	21	21	42	36	39
Teli et al.[29] (1995)	Case series (r)	40	≈2.5 yr	30	10	23	45	20	NA
Pinto et al.[138] (1996)	Case series (r)	32	NA	34	34	28	75	6	55
Laurin et al.[148] (1996)	CT (r)	40	12 mo	70	28	NA	73	NA	NA
George et al.[97] (1998)	Case series (r)	51	NA	NA	NA	NA	49	NA	NA
Angulo et al.[75] (1999)	Case series (r)		NA	60	28	NA	67	NA	27
Matteoni et al.[26] (1999)	Case series (r)	132	Up to 18 yr	NA	22	NA	52	NA	15
Garcia-Monzon et al.[280] (2000)	Case series (r)	41	NA	100	15	15	65	NA	10

r, retrospective; CT, clinical trial, nonrandomized; NA, not applicable.

increases with the degree of obesity, and about 15%–20% of morbidly obese patients (BMI >35 kg/m^2) have NASH.[41,67] Also, numerous reports have documented resolution of a fatty liver following gradual weight loss.[67–70] Subjects with truncal obesity are more prone to develop both diabetes and hypertension as well as fatty liver.[71,72] In one study,[71] the waist-to-hip ratio and male sex accounted for all of the variance in liver fat content. However, obesity is not invariably present in patients with NASH (Table 4), and many individuals with NASH have a normal body weight.[22]

Type 2 diabetes mellitus is a major component of the metabolic syndrome previously noted and is associated with both obesity and NASH.[15,48,49] Both obesity and diabetes are associated with peripheral insulin resistance, hyperinsulinemia, increased free fatty acid levels, and hypertriglyceridemia.[32,61,73,74] Diabetes is not only associated with NAFLD but also may be a risk factor for development of progressive fibrosis.[75]

The metabolic and cellular mechanism(s) linking insulin resistance to NAFLD are not fully understood. Two studies have found decreased insulin extraction by the liver, which contributes to hyperinsulinemia in patients with NAFLD.[76,77]

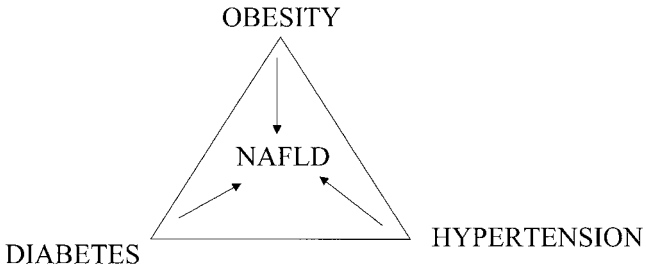

Figure 1. NAFLD as a manifestation of syndrome-X.

Recently, the presence of peripheral insulin resistance, increased free fatty acid levels, increased mitochondrial fatty acid β oxidation, and increased hepatic lipid peroxidation were identified in patients with either fatty liver alone or NASH without cirrhosis.[78] The degree of abnormality was greater in those with NASH. In addition, NASH was also associated with specific mitochondrial abnormalities with intramitochondrial paracrystalline inclusions.[78,79] These, along with studies in experimental models of steatohepatitis,[80,81] are now beginning to provide a framework of understanding linking obesity, insulin resistance, and steatohepatitis.

In addition to the components of the metabolic syndrome previously noted, NAFLD has been associated with several rare disorders of lipid metabolism (e.g., abetalipoproteinemia[82]) and some rare syndromes characterized by severe insulin resistance (e.g., lipoatrophic diabetes and Mauriac syndrome).[73,83] The liver disease in abetalipoproteinemia as well as lipodystrophy can progress to advanced fibrosis and cirrhosis.[82,84–86] NAFLD has also been associated with Weber-Christian syndrome.[87] The biochemical basis for NAFLD in such syndromes and their natural history are unknown and may be variable.

NAFLD has also been described with the use of several drugs (e.g., diltiazem, amiodarone, and tamoxifen).[88–90] There is increasing appreciation of lipoatrophy and severe hyperlipidemia associated with development of fatty liver in patients being treated with highly active antiretroviral drugs (e.g., indinavir).[91–93] This has been associated with the development of severe insulin resistance.[94,95] The incidence, mechanism, and natural history of iatrogenic NAFLD are unknown. Occupational exposure to several types of chemicals (e.g., organic solvents and dimethylformamide) are also associated with fatty liver disease.[96] The prevalence of such exposures and their

impact on the epidemiology of NAFLD are unknown. Until such time that the mechanisms of steatohepatitis in these patient populations and their natural history are resolved, it is best to consider steatohepatitis in these populations separately from most patients with NAFLD.

Iron Overload and NASH

Bacon et al.[22] first reported that many patients (18 of 31) with NASH had biochemical evidence of iron overload. In this series, despite elevation of transferrin saturation and serum ferritin level, the hepatic iron index was <1.9 in all patients. In another study,[97] a serum ferritin level >300 mmol/L was found in 26 of 42 patients (62%), whereas a transferrin saturation >55% was present in 9 of 41 patients (22%) with NASH. Overall, 31% of patients were either homozygous or heterozygous for the Cys282Tyr mutation, values significantly higher than in the general population. However, once again, the hepatic iron index was <1.9 in all. The prevalence of the His63Asp mutation was similar to that in the general population. In yet another study,[98] the prevalence of heterozygosity for either mutation was significantly higher in subjects with NASH compared with controls of similar ethnicity. However, biochemical parameters of iron stores and hepatic iron staining were not significantly different. The significance of the HFE mutations in NASH remains to be fully established. Also, the possibility of referral bias in the reported studies cannot be fully excluded. The presence of iron overload has been reported to be associated with increased hepatic fibrosis.[97] However, these data have been refuted in 2 other series.[75,99]

Symptoms

As with many other types of chronic liver disease, most patients with NAFLD in cross-sectional studies are asymptomatic (Table 4). The liver disease is either discovered incidentally during routine laboratory examination or workup of conditions such as hypertension, diabetes, or morbid obesity. In many asymptomatic subjects, elevated ALT levels are discovered when a hepatic panel is ordered to monitor subjects treated with antihyperlipidemic drugs. Elevated ALT levels or sonographic evidence of fatty liver is sometimes noted during workup of suspected gallstone disease. NAFLD is the most common cause for unexplained persistent elevation of ALT levels once hepatitis C and other known causes of chronic liver disease have been excluded.[100]

Only limited data on symptomatology are available from longitudinal studies, and the likelihood of developing symptoms over time as well as the predictors of future development of symptoms are not known. 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.[22] 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. The development of ascites, anasarca, variceal hemorrhage, or symptoms of hepatic encephalopathy indicates decompensated cirrhosis. Similarly, jaundice occurs late in the course of NASH and indicates advanced liver disease.

Physical 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.[15,22,37,49] The most common finding of liver disease is hepatomegaly, which has been reported in up to 50% of subjects in different studies.[15,22] 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.[48] 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.

Laboratory Abnormalities

In hospital-based populations of patients with NASH, most subjects (50%–90%) have abnormal aminotransferase activities.[15,22,29,49] The degree of enzyme elevation is not marked and is usually between 1 and 4 times the upper limit of normal values (Table 5). Although the ALT levels are higher than aspartate aminotransferase (AST) levels in most instances,[15,48,49,101] the AST level may occasionally be higher than the ALT level, especially in the presence of cirrhosis.[22] However, the AST/ALT ratio is almost never >2. 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. ALT values do not correlate with the degree of steatosis or fibrosis.[39] Although γ-glutamyltransferase levels may be elevated, there are little data on the frequency and degree of elevation. The alkaline phosphatase level may also be variably elevated up to twice the upper limit of normal.[15,22,29,49]

As expected, measures of hepatic functional capacity do not become abnormal until cirrhosis and liver failure set in. 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. Hematologic parameters are usually normal unless cirrhosis and portal hypertension lead to hypersplenism. Across several series,[15,102,103] about 10%–25% of patients have been noted to have a positive antinuclear antibody, a marker of autoimmunity. The significance of this observation is unclear. About 30%–50% of patients with NASH have either diabetes or glucose intolerance.[15,37,49,50,103] A fasting lipid profile shows hypertriglyceridemia in 20%–80% of patients.[15,48–50,103]

Table 5. Histologically Characterized Series of Cases With NAFLD: Laboratory Values

Author (yr)	Study design	n	Mean or median Alk Phos IU/L	Mean or median AST IU/L	Mean or median ALT IU/L	Mean AST/ALT ratio	Mean bilirubin mg/dL	Mean albumin gm/dL	Ferritin ng/mL
1. Hilden (1973)[153]	series (r)	32	n/a	n/a	n/a	n/a	n/a	n/a	n/a
2. Adler (1979)[9]	case series (r)	29	144	100	120	0.83	n/a	n/a	47
3. Ludwig (1980)[15]	case series (r)	20	170	72	38	1.89	0.5	n/a	n/a
4. Itoh (1987)[105]	comparative-case series (r)	16	n/a	114	137	0.83	n/a	n/a	19
5. Diehl (1988)[49]	comparative-case series (r)	39	n/a	n/a	n/a[a]	n/a[a]	n/a[a]	normal	n/a
6, Lee (1989)[50]	case series (r)	49	103	89	104	0.85	0.7	4.2	n/a
7. Powell (1990)[48]	case series (r)	42	108	70	96	0.73	1.18	n/a	n/a
8. Bacon (1994)[22b]	case series (r)	33	139–202	52–122	64–224	n/a	1.5–2.3	n/a	n/a
9. Teli (1995)[29]	case series (r)	40	157	n/a	37	n/a	0.2	n/a	218–1060
10. Pinto (1996)[142]	case series (r)	32	n/a	60	91	0.35	0.7	3.4	n/a
11. Laurin (1996)[152]	nonrandomized CT (r)	40	234 vs. 298	70 vs. 88	113 vs. 93	n/a	0.7 vs. 0.6	n/a	n/a
11. George (1998)[98]	case series (r)	51	n/a	53	96	0.54	n/a	n/a	504
12. Angulo (1999)[76]	case series (r)	144	206	63	82	0.88	0.7	4.3	221
13. Matteoni (1999)[26]	case series (r)	132	n/a	normal	58	n/a	normal	normal	n/a
14. Garcia-Monzon (2000)[280]	case series (r)	46	190	n/a	37	0.81	normal	normal	n/a

r, retrospective; CT, clinical trial nonrandomized.
[a]AST, ALT >3 times upper limit of normal in 30%, AST/ALT >3 in 32%, Bilirubin >2 mg/dL in 17.
[b]Range provided.

How Is NAFLD Diagnosed?

How Good Are the Diagnostic Criteria?

Powell et al.[48] originally proposed 3 criteria for the diagnosis of NASH: (1) a histologic picture of steatohepatitis, (2) convincing evidence of minimal or no alcohol consumption (<40 g/wk), and (3) absence of serologic evidence of viral hepatitis. Although these criteria are used widely in clinical practice, each criterion has specific limitations that bear discussion.

The variability in the histologic expression of NASH has been a source of debate and has prevented the development of a validated and universally accepted set of diagnostic criteria for steatohepatitis. There is also controversy regarding the precise cutoffs in terms of alcohol consumption in the diagnosis of NAFLD. It is generally believed that a fatty liver does not develop with alcohol consumption levels <20 g/day. The original cutoff of <40 g/wk for the diagnosis of NAFLD may therefore be too stringent. However, there are no published and universally accepted threshold levels of alcohol intake that separate alcoholic fatty liver disease from NAFLD.

Determination of the extent of 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.

Random blood alcohol levels have been advocated to determine the extent of alcohol consumption,[104] but it is not always possible to obtain random blood samples. Also, the number of negative tests necessary before a person can be considered not to be an alcohol user is unknown. Furthermore, the optimal interval between such tests remains to be established, and it is not possible to determine the average amount of alcohol consumed over extended periods of time by a single or even 2 random blood alcohol levels.

Several surrogate markers of excessive alcohol consumption over a period of time have also been evaluated. These include serum γ-glutamyltransferase levels,[105] mean corpuscular volume,[105] AST levels, AST/ALT ratio,[106] mitochondrial AST levels,[107,108] and desialylated transferrin levels.[109] The first 4 tests are both widely available and relatively inexpensive. Unfortunately, they lack both sensitivity and specificity, and neither the negative nor positive predictive values are high enough to be clinically useful.[105,106] The clinical utility of the other markers has not been examined outside of a few limited clinical studies. In one such study,[110] desialylated transferrin/total transferrin ratio was found to distinguish between those with alcoholic steatohepatitis versus NASH with greater accuracy than the mitochondrial AST/total AST ratio. It has been reported that plasma pseudocholinesterase levels are elevated in those with a fatty liver[111]; their clinical utility in differentiating between alcoholic steatohepatitis and NASH remains to be defined.

The presence of non-A, non-B hepatitis (hepatitis C) was originally believed to constitute an exclusion criteria for the diagnosis of NASH.[48] Several investigators have now seen patients with hepatitis C who clearly have histologic evidence of a classic steatohepatitis rather than the predominantly portal lymphocytic infiltrate with mild to moderate steatosis seen in hepatitis C.[112] In such cases, the presence of 2 diagnoses (i.e., hepatitis C and NASH) may be considered.

Can NAFLD Be Diagnosed by Noninvasive Methods?

There are no accurate noninvasive methods for the diagnosis of NASH. The presence, degree, and pattern of aminotransferase elevation are nonspecific and do not provide an etiologic diagnosis.[105] Even when the index of suspicion for NASH is high (e.g., in an obese, diabetic individual), the aminotransferase levels do not distinguish between fatty liver alone and NASH.[15,67] The presence of fat in the liver can be diagnosed in many cases using various imaging modalities.

Ultrasonography, computerized tomography (CT) scan, and magnetic resonance imaging (MRI) have all been used to diagnose NAFLD. Of these, sonography is the least expensive and MRI is the most expensive modality. There are 4 sonographic findings of diffuse fatty change in the liver[113]: (1) a diffuse hyperechoic echotexture (bright liver), (2) increased liver echotexture compared with the kidneys, (3) vascular blurring, and (4) deep attenuation. In a small retrospective study,[114] a combination of these parameters allowed diagnosis of fatty liver (defined histologically by fat present in >30% of each lobule) with a sensitivity of 83% and specificity of 100%. Recently, using both 10-MHz as well as 3.5-MHz transducers,[115] frequency-dependent attenuation of an ultrasound beam passed through the liver was shown to correlate well with its fat content.

Liver fat content also can be semiquantitatively estimated by MRI[116] as well as CT scans.[117] Normally, the CT attenuation values for the liver range from 50 to 75 Hounsfield units[113,118,119] when a non–contrast-enhanced scan is obtained. With increasing hepatic steatosis, the liver attenuation values decrease by about 1.6 Hounsfield units for every milligram of triglyceride deposited per gram of liver tissue.[120] 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 in a non–contrast-enhanced scan.[117,119]

When intravenous contrast is used, both the liver and splenic attenuation values increase. However, the hepatic values increase to a lesser degree than the splenic values, thereby increasing the difference in hepatic to splenic values.[121] When a diagnosis of a fatty liver is based simply on a qualitative assessment of the differential attenuation during a contrast-enhanced CT scan, the sensitivity and specificity are 54% and 95%, respectively.[122] Using a cutoff of 20.5 Hounsfield units 80–100 seconds after intravenous contrast injection, a fatty liver could be diagnosed with 86% sensitivity and 87% specificity.[122] At 100–120 seconds, a difference in hepatic and splenic attenuation of 18.8 Hounsfield units had a sensitivity and specificity of 93% each.[122] Thus, the diagnostic accuracy of differential changes in hepatic-splenic attenuation are time dependent and protocol specific. These data have been corroborated by another study in which the sensitivity was even lower (54%–71%).[123] An unenhanced hepatic CT scan remains the optimal CT method for detection of a fatty liver.[122] If hepatic attenuation is higher than the spleen, fatty liver can be excluded with relative confidence.[122] Single-energy CT scans are superior to double-energy CT scans for the determination of fat content, especially when iron overload is also present.[124] By CT imaging,[125] the distribution of the fat is unequal with lower attenuation values in the right lobe compared with the left.

There is considerable interindividual variability as well as intraindividual variability during multiple examinations in the absolute liver attenuation numbers. This is due to nonidentical calibration of different machines, different types of CT scanners, differing regions of interest during multiple examinations, and changes in hepatic fat content. Accurate assessment of fatty liver and changes in hepatic fat content require careful calibration and obtainment of the region of interest at the same level during each examination. The latter requires use of landmarks that move equally with the liver during the various phases of respiration and include the same blood vessels seen in previous examinations. Another way to avoid these confounding variables is to compare the hepatic attenuation values with those of the spleen.

Differences in the precession frequency (3.7 ppm) between water and fat protons can be used in opposed-phase images in which the fat signal is subtracted from the water signal to diagnose fatty liver using MRI.[116,126,127] In such cases, T1-weighted gradient-echo images obtained with echo times 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.[126] Several newer modifications in MRI techniques have resulted in considerable improvement in the ability to diagnose a fatty liver by MRI.[128–133]

In a direct comparison of CT scan with sonography,[124] sonography was found to be more sensitive in detecting fatty change. However, when fatty change is patchy or focal, CT scan and MRI are superior to sonography.[113] Also, when a semiquantitative assessment is required or when multiple comparative studies are planned over time, CT imaging is superior to sonography.

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 versus steatohepatitis. Moreover, diffuse fibrosis is also associated with a hyperechogenic ultrasound pattern and cannot be distinguished from fatty liver with accuracy by ultrasonography. Thus, liver biopsy remains the only accurate way to diagnose steatohepatitis.

What Is the Role of a Liver Biopsy in the Diagnosis of NAFLD?

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. On the other hand, there is little controversy that a liver biopsy is the only accurate method for the diagnosis of NASH,[15,18,22] as shown by the poor positive predictive value

(56%) of clinical and laboratory evaluation for the diagnosis of NASH using histology as the gold standard.[134]

Sorbi et al.[135] 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 diagnosis 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. Importantly, 10 of 12 subjects were offered experimental therapy.

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 (e.g., 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.

Distinguishing Between Alcoholic Fatty Liver Disease and NAFLD

In most instances, it is fairly easy to distinguish alcoholic fatty liver disease from NAFLD. This is particularly true in hospitalized populations, where those with alcoholic hepatitis are usually sicker, have higher serum bilirubin levels, and have an AST/ALT ratio >2.[105,136] The AST/ALT ratio is usually <1 in patients with NAFLD and may be used to differentiate it from alcoholic liver disease.[137] However, in an ambulatory care setting, alcoholic liver disease has also been found to be associated with a similar AST/ALT ratio.[138] The pathologic changes of steatohepatitis are more severe in those with alcoholic hepatitis with greater inflammation, a greater degree of hepatocellular injury, frequent Mallory bodies, and a greater degree of perisinusoidal fibrosis.[136] Those with nonalcoholic liver disease, however, have a greater prevalence of glycogen nuclei. Whereas about 8%–10% of patients with NASH have cirrhosis, 39% of ambulatory and 80%–90% of hospitalized patients with alcoholic hepatitis also have cirrhosis.[136,138] These data indicate that distinction between NAFLD and alcoholic liver disease may not always be easy, particularly in those who consume modest amounts of alcohol. In such cases, reassessment after a period of abstinence may be necessary to establish the diagnosis of NAFLD.

Can Alcoholic Steatohepatitis and NASH Coexist in the Same Patient?

By definition, NAFLD cannot be diagnosed in a subject who consumes excessive amounts of alcohol. However, both alcoholic fatty liver disease and NAFLD commonly occur in the population. It has been shown that the prevalence of a fatty liver is highest in obese individuals who consume excessive alcohol.[42,139,140] It is therefore conceivable that these conditions may occur together in the same individual. However, no reliable methods exist to diagnose both alcoholic fatty liver disease and NAFLD in the same individual. Also, a safe level of alcohol intake that does not accelerate the progression of NASH has not been established. Conversely, a specific threshold level of alcohol intake above which the progression of NASH is accelerated has not been shown. Clearly, more work needs to be done to clarify the relationship between alcoholic fatty liver disease and NAFLD.

Diagnosis of NAFLD in the Setting of Cryptogenic Cirrhosis

Cryptogenic cirrhosis is diagnosed when a specific etiology for cirrhosis cannot be established. Many patients with cryptogenic cirrhosis have risk factors for NAFLD and may indeed have had NASH.[141,142] However, in a given individual, the diagnosis of NASH as a cause of cryptogenic cirrhosis poses several challenges.[143] These include the decrease in hepatic steatosis after development of cirrhosis.[48] Indeed, steatosis may completely disappear. The frequency with which this happens and the time course of disappearance of fat remain to be defined. Also, Mallory bodies rarely are seen and ballooning degeneration is a relatively nonspecific finding. Finally, the presence of centrilobular perisinusoidal fibrosis is not possible in the absence of normal lobular architecture. Thus, the possibility of underlying NASH usually is surmised from a "gestalt" of the constellation of clinical and histologic findings present in an individual case.

What Is the Natural History of NAFLD?

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

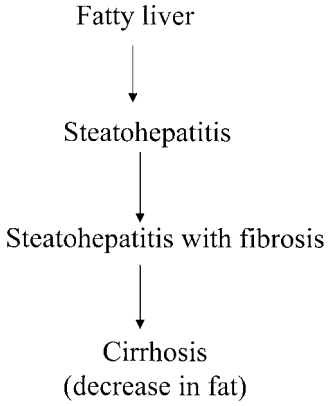

Figure 2. Stages in the progression of NAFLD.

and eventually cirrhosis.[22] It has also been noted that, following development of cirrhosis, fatty change may disappear.[48]

Cross-sectional studies of nonalcoholic fatty liver[15,49] indicate that most subjects have a 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 one study,[29] no instances of progression to steatohepatitis were noted over a 10-year period. Other studies[48,50] also corroborate these data. In contrast, at least one instance of progression from fatty liver alone to steatohepatitis has been noted in a patient after liver transplantation.[143] Also, morbidly obese individuals with a fatty liver alone who undergo rapid weight loss following jejunoileal bypass[144,145] or proximal gastric bypass[67] have been reported to develop steatohepatitis.

At the time of initial presentation, about 30%–40% of patients with NASH have advanced fibrosis,[22,50] whereas 10%–15% have established cirrhosis.[15,22,48,50] Although one study[48] did not find any relationship between the histologic stage and the presence or degree of obesity or diabetes, another study[22] found that those with cirrhosis were more likely to be female (62%) and obese (62%). In a recent large cross-sectional study,[75] 144 subjects with NASH were studied. No fibrosis was found in 26%, whereas 17% had 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.[146]

Assessment of the rate of progression of NASH to NASH with fibrosis and eventually cirrhosis is confounded by the limited data available. The published studies are all retrospective, and few patients have undergone multiple biopsies during follow-up. Powell et al.[48] followed up 42 patients for a median duration of 4.5 years; during this time, 6 of 13 patients showed progression of fibrosis and 1 patient developed cirrhosis. Similarly, 5 of 13 patients developed increasing fibrosis over a mean follow-up of 3.5 years in another study.[50]

In an important report[26] (Table 6), 132 subjects with NAFLD were grouped into 4 categories based on their liver histology: (1) fatty liver alone, (2) fat plus lobular inflammation, (3) fat plus ballooning degeneration, and (4) fat plus ballooning plus either Mallory hyaline or fibrosis. Cirrhosis was present in 4 of 19 subjects in group 3 and 14 of 26 subjects in group 4. A retrospective analysis of survival over 18 years of follow-up showed a 33%, 30%, 26%, and 44% mortality in the 4 groups, respectively. Liver-related deaths were highest in groups 3 and 4; however, even in those with fatty liver alone, 1 liver-related death was reported.

The precise risk of mortality in patients with NAFLD is not known. In the retrospective, cross-sectional series published before 1999,[15,48–50,136,138,147–149] a total of 11 deaths among 299 patients (3.1%) were reported. In a longitudinal study,[48] only 1 of 42 patients died during a median follow-up of 4.5 years, apparently confirming the low mortality noted in cross-sectional studies. However, more recent reports have challenged the notion that NASH is associated with a low (<5%) mortality. In a study of 30 patients with NASH followed up for more than 10 years published only in abstract form,[150] the 5-year survival was only 67% and the 10-year survival was 59%. Although the overall mortality was not significantly different from that of an age- and sex-matched population, the liver-related mortality was increased. In another series,[26] the liver-related mortality was 7 of 54 over an 18-year follow-up in those with fatty liver, ballooning degeneration, and Mallory bodies or perisinusoidal fibrosis. Although most patients with NASH without bridging fibrosis or cirrhosis have a very low risk of death up to 5–10 years from the time of diagnosis, those with more advanced disease are at higher risk of dying as a consequence of their NASH. It is important to note that all of the data available are retrospectively collected and have all of the limitations of such data; there is a critical need for prospective studies in this area.

Many factors may contribute to mortality in patients with NAFLD. These include obesity and diabetes and their complications, other comorbidities associated with obesity and diabetes, and the liver disease itself. There are no published data clearly identifying the relative contributions of these factors to mortality in NAFLD, although one study found that the presence of cirrhosis independently increased the relative risk of mortality.[26] Of the liver-related causes of mortality, the development of liver failure, complications of cirrhosis (e.g., variceal hemorrhage and ascites), and hepatocellular carcinoma can all contribute to mortality. However, the precise incidence of these specific complications is not known.

Histologic improvement may also occur, especially in those with only minimal fibrosis. Following weight loss,[68] the liver histology may improve with a decrease in inflammation, number of Mallory bodies, and even perisinusoidal fibrosis. This is particularly true when the weight loss is achieved slowly and when exercise is part of the weight-loss regimen.[151,152] On the other hand, rapid weight loss may accelerate progression of the disease. In many instances, liver failure becomes manifest during a period of rapid weight loss regardless of its mechanism.[145,153,154]

Table 6. Comparison of Outcomes for Various Histologic Patterns of NAFLD

Variable	Fat alone (n = 49)	Fat + lobular inflammation (n = 10)	Fat + ballooning (n = 19)	Fat + ballooning + Mallory bodies or perisinusoidal fibrosis (n = 54)
Cirrhosis	2	0	4	14
Death	16	3	5	24
Liver-related death	1	0	1	7

NOTE. Based on retrospective analysis of 132 patients with follow-up of up to 18 years.[26]

NAFLD in Selected Patient Populations

NAFLD in Children

NAFLD has been reported in the pediatric population. In a retrospective review of liver biopsy specimens, Baldridge et al.[47] found that 82 of 650 cases had hepatic steatosis, of which 14 were considered to have NASH with varying degrees of fibrosis. Similar data have been reported by others.[30,39,155] Although most reported cases of fatty disorders of the liver in children have been noted around the age of puberty, isolated instances have been reported in those as young as 7–8 years of age.[33] Several studies of obese children[30,38,39] have shown evidence of fatty liver disease, documented by sonography or increased ALT levels, in up to 50%–60% of affected children. Unfortunately, these data have the same limitations as other studies using sonography. However, given that 25%–30% of children in the 6- to 12-year age group and 7%–10% of children in the 12- to 17-year age group are obese,[45,156,157] it is likely that NAFLD is relatively common in the general population.

The clinical picture of NASH in the pediatric population is similar to that in adults. Many children are asymptomatic. The most common symptoms include right upper quadrant aching discomfort and fatigue.[47,158] Obesity and hepatomegaly are the most common physical findings. Most affected children have elevated ALT levels.[47,158] Cirrhosis related to NASH has been described in a 10-year-old child.[155] The duration of obesity may also be a determinant of the likelihood of progression to cirrhosis.[43]

Although NAFLD is an established cause of chronic liver disease in children, many clinical issues remain to be elucidated, including the mechanisms by which it develops, a detailed description of the histology, and the natural history of the disease.

NAFLD in the Morbidly Obese Individual

The recognition of NAFLD as a clinical entity has its origin in descriptions of fatty liver and fibrosis along with variable degrees of inflammation in morbidly obese individuals[5,6,159,160] and the frequent development of progressive liver failure following jejunoileal bypass in these patients.[159,161,162] As early as 1973, Kern et al.[160] described fatty liver in 151 obese subjects, of whom 92 had fibrosis and 6 had cirrhosis. These were followed by other reports of a high incidence of cirrhosis and diabetes in morbidly obese individuals.[9,13,147,163,164] These initial studies led to numerous publications confirming the association of morbid obesity with NASH.[11,139] In a comprehensive review of 1515 morbidly obese patients reported in the literature, Anderson and Gluud[41] noted that fatty change was present in 80% of subjects whereas portal inflammation and fibrosis were present in about 30% of subjects and cirrhosis in 3% of individuals. Obesity has been identified as an independent risk factor for the development of hepatic fibrosis.[26,75]

A characteristic feature of morbid obesity-related steatohepatitis is the development or worsening of steatohepatitis following rapid and massive weight loss usually following jejunoileal bypass.[15,145,161,165–168] When this leads to subacute hepatic failure, it has also been referred to as subacute NASH.[15] The prevalence of hepatic steatosis increased from 66% to 95% in the first year after jejunoileal bypass but returned to baseline values by 5–7 years in one study.[162] During the first 18 months, some patients also show a marked increase in inflammation and hepatocellular injury that may manifest as subacute liver failure.[153] Preoperative perisinusoidal fibrosis is a risk factor for the postoperative development of liver failure and progressive fibrosis.[167,169] It is likely that, in such individuals, surgery precipitates metabolic or other changes that accelerate the hepatocellular injury producing liver failure. Some patients respond to shunt takedown.[153] Glucose-free, amino acid infusions[170] have been reported to improve hepatic steatosis following jejunoileal bypass. Also, improvement in hepatic histology has been reported following treatment with metronidazole.[144]

The dangers of the jejunoileal bypass have led to the use of proximal gastric bypass as the procedure of choice for bariatric surgery.[171,172] Direct comparisons of gastric bypass with jejunoileal bypass show that the former is as efficacious yet safer than the latter.[68,171,172] Recent data indicate that the risks of worsening liver histology are linked to the rapidity of weight loss rather than the type of surgery used. In a carefully performed study, Luyckx et al.[67] studied liver histology before and after gastroplasty in 528 morbidly obese subjects. Following rapid weight loss, the degree of steatosis improved. However, this was associated with an increase in lobular inflammation. Thus, although the risks of subacute liver failure are decreased following gastroplasty, the liver histology may worsen initially. Over time, the hepatic histology improves along with an improvement in parameters of insulin resistance.[173] Gallstones are more prevalent in obese individuals[174] and therefore more likely to occur in those with NASH. Indeed, sonographically diagnosed fatty liver has been associated with an increased prevalence of gallstone disease.[175,176]

NAFLD in Syndromes of Insulin Resistance

There are several distinct clinical syndromes associated with severe insulin resistance that are associated with NAFLD. Diabetes mellitus associated with lipoatrophy is the prototypic example of such a condition.[83,177–179] In such patients, progressive hepatomegaly due to fatty change (fat alone or steatohepatitis with or without fibrosis) occurs frequently. This often causes right upper quadrant discomfort, early satiety, and nausea. Over time, as fibrosis progresses, portal hypertension and splenomegaly can occur. Although the natural history of NASH in syndromes associated specifically with insulin resistance has not been well characterized, progression to cirrhosis can occur.

NAFLD and Hepatitis C

Hepatitis C and NAFLD are both common causes of liver disease. It is therefore not surprising that they can coexist in the same individual. In the presence of hepatitis C, portal and lobular inflammation cannot be used to assess the presence of fatty liver disease. Also, minor degrees of hepatic steatosis often are seen in those with hepatitis C. A confounding factor in published studies is the failure to clearly identify those instances in which fatty liver disease was related to an alcoholic versus nonalcoholic etiology. The degree of steatosis and body mass index are associated with the likelihood of advanced fibrosis.[112,180,181] An association between hepatitis C genotype 3 and hepatitis C core protein with hepatic steatosis also has been described.[182–185] An increase in serum triglyceride levels also occurs during interferon therapy.[186,187] The long-term implications of this phenomenon, if any, are unknown.

NAFLD and Liver Transplantation

Fatty disorders of the liver affect the availability of organs as well as the outcomes of OLT. Recent data[35,188] indicate that up to 20% of potential donors have hepatic steatosis. Hepatic macrovesicular steatosis is associated with primary nonfunction of the graft following OLT, and a survey[189] of 25 liver transplant centers in the United States found that livers with more than 30% fat were discarded by most centers. There are several potential mechanisms that contribute to the poorer function of the fatty grafts, including decreased ability to generate adenosine triphosphate[190] and the generation of toxic metabolites.[191] 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 declaration of brain death. In contrast to macrovesicular steatosis, livers with microvesicular steatosis can be safely used for liver transplantation.[192]

There are only a few small published series of patients with documented NASH who have undergone OLT. NASH has been reported to recur,[193–196] and some patients develop fibrosis within a relatively short period of time. In those with morbid obesity and liver failure precipitated by a jejunoileal bypass, severe NASH with fibrosis has been reported after OLT,[197] necessitating takedown of the bypass. A time-dependent increase in the risk of developing fatty liver after OLT has been found in subjects with cryptogenic cirrhosis with a clinical-histologic phenotype suggestive of NASH[143]; a 100% recurrence of fatty liver occurs by 4–5 years. However, only 3 of 27 subjects developed steatohepatitis and all of the subjects did well clinically.

NAFLD also can develop in those who receive a liver transplant for indications other than NASH. The risk of developing fatty liver is approximately 20% in those who receive a transplant for alcoholic liver disease, hepatitis B, or primary biliary cirrhosis.[143] The development of NAFLD following OLT may be related in part to the weight gain that occurs commonly after transplantation.[198] Such weight gain has been reported to occur mainly between 2 and 16 months after transplantation in most patients.[198] The cumulative steroid dose has also been implicated in the pathogenesis of NAFLD after OLT.[143] The intermediate-term (5–10 years) outcomes of most patients with de novo development of NAFLD after OLT is excellent and, in one study, no instances of graft loss due to NAFLD occurred in this group.[143]

Treatment of NAFLD

The treatment of any condition requires consideration of the natural history of the condition, the relative efficacy and safety of the therapeutic options, and cost. As previously noted, NASH can progress to cirrhosis.[22,75,199] This is particularly true in the presence of bridging fibrosis.[26] Also, those with fat and ballooning degeneration or fat, ballooning degeneration and Mallory bodies or perisinusoidal fibrosis may be at greater risk for progression.[26] Older subjects and those with severe obesity or diabetes are also considered at risk for more advanced disease.[75] These factors must be kept in perspective when considering the therapeutic options for a given patient.

There are no published controlled trials of treatment modalities for NAFLD. It is therefore not possible to make any statements on relative risk of improvement with any modality. In the absence of treatment modalities of proven efficacy, therapy is directed toward correction of the risk factors for NASH (i.e., insulin resistance, decreasing delivery of fatty acids to the liver, and use of drugs with potentially hepatoprotective effects).

Treatment of Risk Factors

Weight management. There are several small anecdotal reports of improvement in liver histology following weight loss.[67–70] However, there are no randomized clinical trials of weight control as a treatment of NAFLD. In overweight individuals with elevated aminotransferase levels, weight reduction by 10% or more has been shown to correct aminotransferase activities and decrease hepatomegaly.[200] Despite the absence of randomized studies, obese subjects with NAFLD require weight management because of the benefits of weight loss on their cardiovascular risk profile.

The National Heart, Lung, and Blood Institute (NHLBI) and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) clinical guidelines for the management of obesity provide specific recommendations for the selection of adult subjects for weight-loss treatment.[201] In children, an expert committee from the Maternal and Child Health Bureau, Department of Health and Human Services, has recommended that those with a BMI greater than the 95th percentile or greater than the 85th percentile with complications of obesity should be evaluated for treatment.[202] In such patients, it is important to exclude genetic and endocrine disorders associated with obesity.

The NHLBI-NIDDK expert clinical guidelines for weight loss recommend that the initial target for weight loss should be 10% of baseline weight.[201] It is important to note that most weight-loss regimens can achieve a modest 5%–10% weight

loss.[203–205] This results in considerable improvement in insulin sensitivity[206,207] and cardiovascular risk profile.[205,208] Very rapid weight loss may cause worsening of steatohepatitis and may precipitate liver failure.[67] Also, the risk of gallstone disease increases exponentially when the rate of weight loss exceeds 1.5 kg/wk.[209] The NHLBI-NIDDK guidelines further suggest that weight loss should proceed at a rate of 1–2 lb/wk.[201] Several studies have shown that the risk of development of gallstones during weight loss can be decreased with the use of ursodeoxycholic acid (UDCA).[210–213] In morbidly obese individuals undergoing rapid weight loss, the use of UDCA for prevention of gallstones has been shown to be cost-effective.[214] The fear of potential adverse health consequences of weight cycling during attempts at modest weight loss (up to 10% of baseline) in unselected populations of obese patients is unproven and should not deter attempts to achieve such weight loss.[215]

The NHLBI-NIDDK clinical guidelines for weight loss do not make any specific recommendation about monitoring liver functions while a patient undergoes weight loss. In patients with NAFLD, it would seem prudent to monitor for liver dysfunction, especially when the weight loss is rapid and severe (>2.5 lb/wk). Although there are no data on which to base scientific recommendations about the frequency of such monitoring, many experts check liver function tests once a month.

Diet is an important component of any weight-loss regimen. Saturated fats in the diet worsen insulin resistance,[216–218] whereas dietary fiber can improve insulin resistance.[219,220] There are no controlled studies of the value of diet in the management of NAFLD. Dietary supplementation with polyunsaturated fatty acids may improve insulin sensitivity and cardiovascular risk profile.[221–223] However, the effects of such a dietary modification on NAFLD are unknown. The roles of specific fiber supplements designed to decrease insulin resistance or dietary fat have not been evaluated.

In the absence of clinical trials that specifically address the value of dietary modification in NAFLD, it seems prudent to recommend a heart-healthy diet as recommended by the American Heart Association[224] for those without diabetes or a diabetic diet as recommended by the American Diabetes Association[225] for those with diabetes. Several systematic reviews and guidelines for the management of obesity have been published in the past 5 years.[201,202,226–230] Readers are referred to these for a detailed analysis of the value of dietary modification for weight loss. Dietary changes alone often are associated with a high failure rate in achieving and maintaining weight loss.[207,223,231] The specific psychological, social, cultural, and economic factors responsible for this are yet to be defined. Dietary modification is most likely to be successful when accompanied by behavior-modification therapy,[201,230] including cognitive-behavioral modification and hypnosis-based therapies.[232,233]

The value of exercise in achieving and maintenance of weight loss is now well established.[234–240] Exercise has been shown to increase the oxidative capacity of muscle cells and utilization of fatty acids for oxidation.[241] This decreases fatty acid and triglyceride accumulation in the myocytes and thereby improves insulin sensitivity.[242] The degree of improvement in insulin sensitivity is related to the intensity of the exercise.[243] However, a recent meta-analysis of clinical trials of exercise did not find sufficient evidence to prove that physical activity altered the dyslipidemia associated with obesity.[244] Also, exercise alone is insufficient to achieve and maintain weight loss in many subjects.[205] However, when weight loss can be achieved, this can be associated with improved hepatic histology.[70,151,245] Several studies that have evaluated the success of nonpharmacologic approaches to weight loss have recently been reviewed.[246] Physician-oriented strategies are associated with the poorest outcomes, whereas partner-oriented strategies and a structured approach to weight loss are associated with the best outcomes. Patient-oriented strategies have intermediate results. Both aerobic exercise and resistance training have been shown to be beneficial in reducing weight.[204,245] Intermittent exercise also has been found to be as effective as daily exercise in a randomized controlled trial involving obese women.[247]

The role of weight-reducing pharmacologic regimens in NAFLD also remains to be studied. Currently, 3 drugs are approved for weight reduction: phentermine, sibutramine, and orlistat. Although the value of these drugs in achieving weight loss is established,[248–255] their value in the management of NAFLD remains to be shown. The NHLBI-NIDDK guidelines for management of obesity recommend that pharmacotherapy be considered as an adjunct to lifestyle modification for patients with a BMI $\geq$30 kg/m^2 and no concomitant obesity-related risk factors or diseases.[201] Pharmacotherapy may also be considered in those with a BMI $\geq$27 kg/m^2 with concomitant risk factors or diseases such as hypertension, dyslipidemia, coronary artery disease, type 2 diabetes mellitus, and sleep apnea. Sibutramine should not be used in those with a history of hypertension, coronary artery disease, congestive heart failure, arrhythmias, or history of stroke. Morbidly obese subjects (BMI $\geq$35 kg/m^2) may be considered for more aggressive weight-loss programs, including proximal gastric bypass. This operation has been shown to be superior to vertical-banded gastroplasty as well as jejunoileal bypass.[172,256–262] However, such patients should be evaluated carefully before starting any therapy for both the presence of other obesity-related diseases as well as their risk of developing decompensated liver disease during rapid weight loss. Such risks must be integrated with the clinical profile of the patient to develop an individually tailored treatment plan for each patient.

Pharmacologic treatment of insulin resistance. Insulin resistance seems to be the common denominator in many cases of NASH. NASH is associated with decreased insulin-mediated suppression of lipolysis.[78] Consequently, subjects with NASH have high serum-free fatty acid concentrations, allowing greater hepatic fatty acid uptake and oxidation. Increased fatty acid delivery to the liver also may have complex effects within the hepatocytes, including interference with insulin function,[263–266] preferential utilization of fatty acids for mitochondrial oxidation,[78,267] and the proapoptotic

Table 7. Treatment Trials in NAFLD

Author	Intervention	n	Design	Control	End point	Effect
Lavine[276]	Vitamin E	11	Case series	Uncontrolled	ALT	Improvement
Obinata et al.[27]	Taurine	10	Case series	Uncontrolled	ALT	Improvement
Laurin et al.[148,a,b,c]	UDCA vs. clofibrate	24:16	Nonrandomized comparative	UDCA vs. clofibrate	ALT, histology	Improved No effect on hepatitis Improved 9/10
Caldwell et al.[272]	Troglitazone	10	Case series	Uncontrolled	ALT, histology	Decreased inflammation 7/10
Marchesini et al.[271]	Metformin	20	Case series	Uncontrolled	ALT	Improvement
Abdelmalek et al.[278]	Betaine	10	Case series	Uncontrolled	ALT, histology	Improvement in ALT and histology
Miglio et al.[279]	Betaine[d]	191	Randomized controlled	Placebo	ALT, histology	Improvement in ALT and histology

[a]5/24 normalized ALT.
[b]Only those whose weight decreased showed decreased ALT.
[c]The degree of improvement in inflammation was 1 grade in most subjects.
[d]Treatment arm received betaine + ethanolamine + nicotinamide; treatment duration was only 8 weeks.

mitochondrial uncoupling protein 2 expression.[268,269] These, along with other potential intrahepatic abnormalities, culminate in the development of steatohepatitis. These considerations, along with the well-known association of NASH with obesity and diabetes, have led to attempts to treat NASH by treating insulin resistance.

There are no controlled data on the use of pharmacologic agents for the management of NASH by improving insulin resistance (Table 7). There are 2 classes of drugs that have been shown to correct insulin resistance: (1) biguanides (e.g., metformin) and (2) thiazolidinediones (e.g., rosiglitazone and pioglitazone). The former work by mechanisms that are undefined. In an animal model of steatohepatitis, treatment with metformin improved hepatic steatosis and inflammation.[270] In a recent study, metformin was associated with an improvement in serum aminotransferase activities.[271] However, no histologic data were provided. The use of this drug remains experimental.

Thiazolidinediones are drugs that act via peroxisome proliferator activated receptor γ and improve insulin sensitivity. A small nonrandomized series of patients with NASH were treated with troglitazone for up to 6 months.[272] Of the 10 subjects studied, 1 had diabetes and 3 had cirrhosis. Following treatment, mean ALT values improved in 9 of 10 subjects and the inflammatory scores improved from moderate to mild in 5 subjects. The inflammatory score worsened in 1 patient but remained the same in another. Although these initial data are interesting, caution must be exercised in interpreting the data due to the possibility of error because of the low number of subjects studied. Moreover, the study was not long enough to study any effects on hepatic fibrosis, and troglitazone has now been withdrawn from the market due to its hepatotoxicity. In another study in which troglitazone was used in 13 patients with diabetes with lipodystrophy, there was a decrease in serum free fatty acid levels but no changes in visceral fat were noted.[273] However, liver histology was not examined and 1 patient developed troglitazone hepatotoxicity, which required discontinuation of the drug. It is also worth noting that the effects of different drugs on the insulin sensitivity of various metabolic pathways are variable.[274] Thus, data from one agent may not be applicable to another agent. Despite these limitations, these studies set the stage for future trials using other thiazolidinediones.

Lipid-Lowering Agents

Hypertriglyceridemia is often associated with NASH. In one controlled trial,[148] clofibrate had no beneficial effects on liver functions or hepatic histology; in another small controlled trial, gemfibrozil improved liver chemistry.[275] However, no histologic data are available from the latter study. Thus, in general, such agents are not used for the treatment of patients with NASH. Based on the current understanding of the pathogenesis of NAFLD, there is no rationale for the use of 3-hydroxy-3-methylglutaryl–coenzyme A reductase inhibitors for the treatment of patients with NAFLD. There also are no data on the use of such drugs for NAFLD.

Drugs That Protect Hepatocytes

Several drugs believed to be hepatoprotective have been used in patients with NASH. These include UDCA, betaine, vitamin E, lecithin, β-carotene, and selenium. Of these, peer-reviewed published data are available on betaine, UDCA, and vitamin E.

To date, there is only one published series of 11 pediatric patients with NASH who received vitamin E (DL-α-tocopherol) 400 IU/day orally.[276] The baseline ALT levels were elevated in all subjects. The dosage was increased if the ALT level remained elevated, and ultimately a dosage varying from 400 to 1200 IU/day was used. During a mean follow-up of 5.2 months, the ALT level either improved markedly or normalized in all cases. Although these data are encouraging, the potential weakness of this study is the lack of histologic confirmation of NASH before therapy or of improvement after therapy.

The value of UDCA, a hydrophilic bile acid with hepatoprotective properties, on NASH was examined in a controlled trial.[148] Use of UDCA was associated with improved liver

enzyme levels and a decrease in hepatic steatosis. However, the long-term effects and optimal dose of UDCA have not been established. The usual dose of UDCA is 10–15 mg · kg^{-1} · day^{-1} orally. In another single uncontrolled series, 10 children treated with taurine supplements orally had radiologic resolution of their fatty liver.[277] Radiologic improvement was accompanied by a decrease in glycine/taurine-conjugated bile acids.

In 2 recent studies,[278,279] betaine supplements were given for the treatment of patients with NASH. Betaine is a precursor of *S*-adenosyl methionine, a hepatoprotective factor. In one study,[278] 10 subjects received betaine anhydrous for 12 months in 2 daily divided doses. Seven of 10 subjects completed 1 year of treatment. In this group, an improvement in aminotransferase activity as well as liver histology was noted. Similarly, a 25% improvement in hepatic steatosis was reported in a randomized controlled study in which betaine was administered along with diethanolamine glucuronate and nicotinamide ascorbate for 8 weeks.[279] These findings now require confirmation in large, long-term prospective trials.

There are no data to support or refute the use of phlebotomy for those with NASH. If used at all, it should be restricted to those with documented evidence of iron overload.

Summary

NAFLD is a major cause of liver-related morbidity in North America. It is frequently associated with the presence of insulin resistance. There is increasing evidence that NAFLD can progress to cirrhosis and liver failure. Physicians should actively check for the presence of NAFLD in those who are overweight and/or diabetic. There is no established treatment for NAFLD. Treatment usually is directed toward optimizing body weight. The role of pharmacologic agents remains to be established, and much more work is necessary to define the pathogenesis of this condition and to develop effective treatment.

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