Nonalcoholic Fatty Liver Disease as a Complication of Insulin Resistance
Manal F. Abdelmalek, MD, MPH*, Anna Mae Diehl, MD
Division of Gastroenterology, Hepatology, and Nutrition, Duke University Medical Center, P.O. Box 3913, Durham, NC 27710, USA

Nonalcoholic fatty liver disease (NAFLD) spans a spectrum of hepatic pathology from hepatic steatosis (Fig. 1A) at the most clinically benign end, through an intermediate lesion—nonalcoholic steatohepatitis (NASH) (Fig. 1B), to cirrhosis (Fig. 1C) at the opposite end of the disease spectrum [1–4]. Liver cell injury in NASH is often accompanied by spotty lobular infiltration with inflammatory cells, and sometimes with fibrosis. Hepatocyte injury and inflammatory cell infiltration generally are worse in the perivenous areas of the liver than in the periportal areas. Interestingly, cirrhotic livers that result from NAFLD may have relatively little steatosis or inflammation. Thus, based on histologic findings and negative testing for other causes of liver disease, many of these cases were once considered “cryptogenic” [5]. Although the pathogenesis is actively being investigated, NAFLD is currently considered the hepatic manifestation of the metabolic syndrome [6]. To formulate an approach to diagnosis and treatment, it is first important to understand the epidemiology, natural history, pathogenesis, and clinical features of NAFLD.

Epidemiology

Triglyceride accumulation in the liver (hepatic steatosis), the hallmark of NAFLD, can be identified by abdominal imaging techniques, providing...
a fairly convenient noninvasive means to estimate the prevalence of fatty liver in the general population. A recent proton-nuclear magnetic resonance (NMR) spectroscopy study of over 2000 adults in one urban area in the United States suggests that values for liver triglyceride content are 5.5% or lower in healthy, nonobese individuals [7]. If values above this cutoff are considered to reflect abnormal hepatic accumulation of fat, about a third of the general population has hepatic steatosis. Other work suggests that the overall combined prevalence of chronic hepatitis C, hepatitis B, and alcohol-associated liver disease accounts for fewer than 20% of serum alanine aminotransferase (ALT) elevations in the general United States population [8]. Hence, NAFLD is currently the leading cause of chronic liver disease in the United States. Certain subgroups have an even higher prevalence of NAFLD than the general population [9]. The risk of NAFLD is increased in individuals who have type 2 diabetes [10,11], with abdominal sonography demonstrating that at least half have hepatic steatosis [12]. Other population-based studies, such as the Third National Health and Nutrition Examination Survey (NHANES III), [8,13] and the Dallas Heart Study [7],

Fig. 1. Photomicrographs of (A) macrovesicular steatosis, (B) steatohepatitis with pericellular fibrosis, and (C) macronodular cirrhosis that demonstrate the range of NAFLD. (Courtesy of M Gottfried, MD, Durham, NC, and C Liu, MD, PhD, Gainesville, FL.)
confirm that type 2 diabetes is highly correlated with NAFLD. The likelihood of having NAFLD is also directly proportional to body weight [1]. Therefore, it is not surprising that most patients undergoing bariatric surgery for morbid obesity have NAFLD (37%–93%), NASH (26%–44%), and rarely, bridging fibrosis or cirrhosis (2%–9%), demonstrated by intraoperative liver biopsy [14–16].

**Natural history and prognosis**

Although emerging evidence suggests that NAFLD is likely to be one of the most common causes of cirrhosis in the United States and several other countries, skepticism persists about its clinical significance. Recent studies are helping to dispel the belief that NAFLD is a benign disease. In the population-based study cited earlier [17], individuals with a diagnosis of NAFLD had a higher overall rate of mortality compared with age-, gender-, and body mass index (BMI)-matched controls who did not have NAFLD. Liver disease contributed significantly to this difference, being the third leading cause of death in NAFLD patients, compared with the thirteenth cause of death in those without this diagnosis. Overall, about 5% of patients who have NAFLD develop cirrhosis over an average of a 7-year period, with 1.7% dying of complications of liver cirrhosis [17]. Although the likelihood of developing cirrhosis is low, the high prevalence and chronic nature of NAFLD translates to a significant health burden for the general community.

One relatively unique feature that distinguishes patients who have cirrhosis caused by NAFLD from those who have cirrhosis caused by other liver diseases is that patients who have NAFLD-related cirrhosis are more likely to have other, serious end-organ complications of the metabolic syndrome, particularly type 2 diabetes, cardiovascular disease, and non-liver cancers. Indeed, as in other individuals who have the chronic metabolic syndrome, the two leading causes of death are cardiovascular disease and cancer in individuals who have NAFLD. There is growing evidence that NAFLD contributes to the pathogenesis of the systemic insulin resistance syndrome. Thus, even in the absence of cirrhosis, NAFLD probably plays some role in the two leading causes of mortality that eventually ensue from long-term consequences of the metabolic syndrome.

Although relatively few long-term follow-up studies of patients who have NAFLD have been reported, the accumulating data about liver-specific outcomes are very consistent [17–22]. First, it is apparent that in NAFLD, as in other liver diseases, liver-specific morbidity and mortality are largely restricted to individuals who develop cirrhosis. Second, as in other liver diseases, patients who have NAFLD-related cirrhosis are more likely to have other, serious end-organ complications of the metabolic syndrome, particularly type 2 diabetes, cardiovascular disease [23], and non-liver cancers.
Third, patients who have advanced fibrosis caused by NAFLD are at risk for hepatocellular cancer (5-year cumulative incidence as high as 20%) and death from liver disease (10-year liver-related mortality rates as high as 11%). Fourth, like many other causes of chronic hepatitis, NAFLD often recurs after liver transplantation [24].

Clinical diagnosis and evaluation

Clinical manifestations

NAFLD is the hepatic manifestation of the insulin resistance (metabolic) syndrome. Risk factors underlying “primary” NAFLD include obesity [25,26], type 2 diabetes mellitus (DM) [12], dyslipidemia, hypertriglyceridemia [27], history of cyclic weight gain and loss [28], and hypertension [29]. Each of these conditions also conveys a risk for cardiovascular disease. Thus, treatment of patients who have NAFLD should aim to identify and treat associated metabolic factors such as obesity, glucose intolerance, dyslipidemia, and hypertension. Although the frequent association of NAFLD with the metabolic syndrome is well-known [30,31], the metabolic syndrome is now recognized as a strong predictor of the presence of NAFLD [32,33] and progressive fibrosis. The worldwide increase in obesity and the metabolic syndrome [34] has paralleled the worldwide increase in NAFLD [34–38].

Before making a diagnosis of “primary” NAFLD, secondary causes of NAFLD should also be considered and excluded when evaluating a patient who has elevated serum aminotransferases (Box 1). Use of alcohol and medications that cause hepatic steatosis (Box 2) should also be ascertained with a detailed medical history. Finally, the presence of NAFLD should also be considered in those who have persistent elevation of serum ALT levels for which another cause cannot be found.

Patients who have NAFLD are generally asymptomatic, although some report fatigue or right upper quadrant abdominal discomfort. The right upper quadrant discomfort may be mistaken for irritable bowel syndrome or gallbladder disease. Hepatomegaly is commonly noted on physical examination. Patients who have NAFLD are subject to health problems directly relating to the carriage of excess adipose tissue (ie, arthritis, nonspecific bodily aches and pains, sleep disturbance, dyspnea on mild exertion, excessive sweating, social stigmatization and discrimination) that may contribute to low quality of life and depression. Patients who have advanced liver disease may present with manifestations of muscle wasting, jaundice, gastrointestinal bleeding, or ascites. By definition, most patients do not consume a significant amount of alcohol. Although is debatable what constitutes “significant” alcohol intake, consumption of fewer than 2 drinks (20 g) per day in men and 1 drink (10 g)/day in women has been suggested as a cutoff [3].
Aside from abnormalities in serum glucose, cholesterol, and triglycerides, abnormal liver enzymes are frequently noted in patients who have NASH; however, liver enzymes are insensitive for the detection of NAFLD, and may be normal in up to 78% of patients. Among patients who have normal

---

**Box 1. Secondary causes of nonalcoholic fatty liver disease**

*Inborn errors of metabolism*
- Abetalipoproteinemia
- Andersen’s disease
- Cholesterol ester storage disease
- Familial hepatosteatosis
- Galactosemia
- Glycogen storage disease
- Hereditary fructose intolerance
- Hypobetalipoproteinemia/dysbetalipoproteinemia
- Lipoatrophy or lipodystrophy
- Mauriac syndrome
- Refsum’s syndrome
- Schwachman syndrome
- Systemic carnitine deficiency
- Tyrosinemia
- Weber-Christian syndrome
- Wilson’s disease

*Nutritional*
- Gastrointestinal surgery for morbid obesity
- Severe starvation or cachexia
- Kwashiorkor and marasmus
- Refeeding syndrome
- Total parenteral nutrition
- Protein malnutrition

*Infection*
- HIV Infection
- Hepatitis C viral Infection (genotype 3)
- *Bacillus cereus* toxin
- Bacterial overgrowth

*Miscellaneous*
- Inflammatory bowel disease
- Acute fatty liver of pregnancy
- Short bowel syndrome
- Wolman’s disease
- Environmental hepatotoxin exposure

---

Aside from abnormalities in serum glucose, cholesterol, and triglycerides, abnormal liver enzymes are frequently noted in patients who have NASH; however, liver enzymes are insensitive for the detection of NAFLD, and may be normal in up to 78% of patients. Among patients who have normal
ALT levels, the full histological spectrum of disease may be present [39]. When present, liver enzyme elevations are generally restricted to ALT and aspartate aminotransferase (AST). Glutamyltransferase and alkaline phosphatase may or may not be mildly elevated. Elevations of AST and ALT are typically within 1.5 times the upper limit of normal levels, and rarely exceed 10 times the upper limit of normal [40]. Such elevations should prompt further evaluation for acute hepatitis or acute on chronic liver injury. Hyperglycemia (caused by the association with diabetes) is present in one third of patients. Hyperlipidemia (usually triglycerides) is present in

Box 2. Medications known to cause nonalcoholic fatty liver disease

*Retroviral agents*
- Zidovudine
- Didanosine
- Fialuridine

*Antibiotics*
- Azaserine
- Bleomycin
- Puromycin
- Tetracycline

*Cytotoxic/cytostatic drugs*
- Azacitidine
- Azauridine
- L-asparaginase
- Methotrexate

*Other drugs*
- Amiodarone
- Aspirin
- Calcium channel blocker
- Cocaine
- Ethyl bromide
- Glucocorticoids
- Heavy metals
- Hydrazine
- Hypoglycin
- Orotate
- Perhexiline maleate
- Synthetic estrogens
- Tamoxifen
- Valproic acid
approximately 20% to 25% of patients. Immunoglobulin A level may be elevated in about 25% of patients. Antinuclear antibody titer is positive in about one third of patients, and does not necessarily represent the presence of a coexistent autoimmune condition. Abnormal iron indices are common, but generally do not indicate genetic hemochromatosis. Clinical evaluation should focus on the presence of metabolic risk factors, as well as risk factors for advanced hepatic fibrosis such as age greater than 45 years, diabetes, elevated BMI, an AST/ALT ratio greater than one, or thrombocytopenia [40].

**Hepatic imaging**

Once ongoing alcohol use (>20 g/day) and other common causes of liver disease are excluded by clinical and laboratory evaluation, the liver is usually imaged by sonography, CT scan, or MRI. These modalities can be used to determine the presence of biliary tract disease and focal liver disease, which may be responsible for elevation of liver enzyme levels. Magnetic resonance spectroscopy has the advantage over the other commonly used imaging modalities of sonography, CT, and MRI for the assessment of hepatic steatosis, because it is quantitative [41]; however, none of these diagnostic studies distinguish between fatty liver, NASH, and NASH with fibrosis, and therefore cannot be used to make these distinctions [42]. Although sonography is slightly more sensitive for detecting hepatic steatosis, CT scan is more specific but more expensive. Sufficient data on the comparative assessment of these tests on which to base a recommendation, including their cost and predictive values, are lacking. Hence, a recommendation about the use of one modality versus another cannot be made at this time. It is, however, common practice to use either sonography or CT scan in the diagnostic evaluation of presumptive NAFLD.

**Histology and role of liver biopsy**

The diagnosis of NASH, as opposed to benign steatosis, and its grade and stage can only be made with precision by a liver biopsy [43]. A grading and staging scheme (Box 3) was recently published [44] and is currently being validated by the NASH Clinical Research Network. Hepatocyte injury and inflammatory cell infiltration generally are worse in the perivenous than in the periportal areas of the liver. The pattern of fibrosis is typically pericellular and sinusoidal (dubbed “chicken-wire” fibrosis). As cirrhosis evolves, fibrous septa bridge portal and perivenous areas (see Fig. 1B).

Histologic endpoints are important in therapeutic trials and for translational research efforts focused on defining the pathophysiology of this condition. The role of liver biopsy in NAFLD in routine clinical care has been debated. A liver biopsy can confirm the diagnosis of NASH, discern the presence of fibrosis or cirrhosis, and exclude other forms of chronic liver disease [45,46]. A liver biopsy does carry a small risk of morbidity and mortality,
Box 3. Proposed grading and staging of NAFLD

Benign steatosis
Mild: <33% steatosis
Moderate: ≥33% and ≤66% steatosis
Severe: >66% steatosis

Nonalcoholic steatohepatitis
Grade 1, mild
Steatosis: predominantly macrovesicular, ranges from less than 33% to up to 66% of the lobules
Ballooning: occasionally observed; zone 3 hepatocytes
Lobular inflammation: scattered and mild acute (polymorphs) and chronic inflammation (mononuclear cells)
Portal inflammation: none or mild

Grade 2, moderate
Steatosis: any degree, usually mixed macrovesicular and microvesicular
Ballooning: present in zone 3
Lobular inflammation: polymorphs may be noted associated with ballooned hepatocytes, or pericellular fibrosis; greater than mild chronic inflammation
Portal inflammation: none, mild to moderate

Grade 3, severe (florid steatohepatitis)
Steatosis: usually >66% (zone 3 or panacinar); commonly mixed steatosis
Ballooning: predominantly zone 3; marked
Lobular inflammation: scattered acute and chronic inflammation; polymorphs may appear concentrated in zone 3 areas of ballooning and perisinusoidal fibrosis
Portal inflammation: mild or moderate; not predominant or marked
Staging (requires Masson’s trichrome or equivalent stain): a separate portal-based process with sparing of zone 3 has been proposed, but remains to be established or refuted

Fibrosis stage
Stage 1: zone 3 perivenular, perisinusoidal, or pericellular fibrosis; focal or extensive
Stage 2: as for stage 1 plus focal or extensive portal fibrosis
Stage 3: bridging fibrosis, focal or extensive
Stage 4: cirrhosis with or without residual perisinusoidal fibrosis

and is expensive. In the absence of US Food and Drug Administration (FDA)-
approved therapies for NAFLD, with the exception of those patients who
have advanced fibrosis (stage F3–4), knowing the histology may not alter cli-
cical care of individual patients. Therefore, the decision to perform a biopsy in-
volves an assessment of the specific clinical circumstances in a given individual
who is suspected to have NAFLD. The cost and risks of the biopsy are gener-
ally weighed against the value of the information obtained from the biopsy in
estimating prognosis and guiding future management decisions. A reasonable
approach to a patient who is suspected to have NAFLD is clinical practice is to
consider a liver biopsy in those patients at increased risk for having fibrosis.
Such patients are those who have the metabolic syndrome, and those patients
who have persistently elevated liver enzymes despite optimal management of
associated metabolic conditions such as obesity, diabetes, or hyperlipidemia.
Obesity, older age, diabetes, and an AST:ALT ratio greater than 1 have been
associated with advanced fibrosis [40,47]. Assuming no absolute contraindi-
cations to the procedure, a liver biopsy should also be considered in patients who
have clinical features suggestive of advanced liver disease (ie, mild thrombocy-
topenia, hypoalbuminemia, hyperbilirubinemia, or altered liver contour on
imaging). A diagnostic algorithm is outlined in Fig. 2.

**Pathogenesis: nonalcoholic fatty liver disease as a complication of insulin
resistance**

Over the last decade, considerable progress has been made in delineating
the mechanisms that cause steatosis and steatohepatitis [48]; however, it

---

**Fig. 2.** Diagnostic approach to evaluation of NAFLD. IRS, insulin resistance syndrome;
AFLD, alcoholic fatty liver disease; *, cutoff for women is >10 g/day.
remains less evident why only a minority of individuals who have these “early” stages of fatty liver disease progress to cirrhosis or develop liver cancer. In the early stages of NAFLD, fat accumulates within hepatocytes when mechanisms that promote lipid disposal (lipoprotein secretion and fatty acid oxidation) cannot keep pace with mechanisms that promote lipid uptake and biosynthesis. Increased hepatocyte accumulation of triglyceride (TG), the hallmark of NAFLD, is closely linked to insulin resistance. Insulin resistance increases lipolysis of peripheral adipose tissue, with resultant increased fat influx into the liver in the form of free fatty acids (FFA). Furthermore, hyperinsulinemia promotes de novo TG synthesis within the liver and inhibits free fatty acid oxidation. Hepatic TG accumulation results from alterations of factors (hepatic and systemic) that control the balance between hepatic lipid input (ie, uptake and synthesis), and output (ie, oxidation); however, the mechanisms driving TG accumulation differ among individuals and within a given individual at different points in time. In turn, these differences in steatosis pathogenesis prompt heterogeneous compensatory responses that exert different outcomes on hepatocyte viability. Studies of different rodent models of NAFLD support the concept that liver injury in NAFLD results from hepatocyte accumulation of FFA and the associated cellular stress responses that develop as fatty cells attempt to dispose of the excess lipids [48].

Three of the best-characterized factors that modulate the evolution of fatty liver disease are fatty acids, tumor necrosis factor alpha (TNFα), and adiponectin [49–51]. In addition to modulating lipid homeostasis, various adipocytokines also regulate carbohydrate metabolism by influencing cellular sensitivity to insulin. Fatty acids routinely traffic between the liver and adipose tissues that are important sources of TNFα and adiponectin [52]. Interestingly, the latter two proteins regulate fatty acid turnover within hepatocytes. Adiponectin generally reduces lipid accumulation within hepatocytes by inhibiting fatty acid import and increasing fatty acid oxidation and export. Adiponectin is also a potent insulin-sensitizing agent [53]. TNFα antagonizes the actions of adiponectin, and thereby promotes hepatocyte steatosis and insulin resistance [53]. Moreover, the severity of NAFLD-related liver damage parallels the severity of insulin resistance, with cirrhosis and liver-related mortality being greatest in patients who have DM [54,55]. Despite the apparent robustness of this clinical correlation, it has been difficult to understand whether the association between NAFLD and DM reflects the negative outcomes of inhibiting insulin actions in the liver itself, or NAFLD results from loss of insulin activity in extra-hepatic tissues. If hepatic (rather than systemic) insulin resistance is in fact the driving force for NAFLD, this might explain why systemic insulin resistance is not a prerequisite for hepatic steatosis [55]. On the other hand, it does not clarify why many humans and experimental animals who have NAFLD exhibit both increased rates of hepatocyte lipid synthesis (suggestive of enhanced hepatic insulin activity), and hyperinsulinemia with excessive
hepatic glucose output (typical of hepatic insulin resistance). The latter findings suggest that differential inhibition of various insulin-regulated signaling pathways within hepatocytes might be necessary for NAFLD pathogenesis.

The confusing role of insulin resistance in NAFLD pathogenesis/progression has not been resolved by studies of animal models of NAFLD. Indeed, such work only underscores the complexity of this relationship. Similar to many obese humans, leptin-deficient (ob/ob) and leptin-resistant (db/db) murine models of NAFLD exhibit hyperinsulinemia, hyperglycemia, and evidence of both systemic and hepatic insulin resistance [56]. Treatment with insulin sensitizing agents has been beneficial, albeit inconsistently. On the other hand, methionine and choline deficient (MCD) diet-fed mice develop NASH and progressive hepatic fibrosis despite diet-induced decreases in serum insulin and glucose, suggestive of enhanced systemic sensitivity to insulin. Nevertheless, insulin-sensitizing agents also seem to improve MCD diet-induced liver disease [57]. Recent evidence of reduced insulin receptor and insulin receptor substrate 2 (IRS2) tyrosine phosphorylation in the livers of MCD diet-fed mice supports the possibility that these animals have hepatic insulin resistance [58]. On the other hand, mice who have hepatocyte-specific activation of protein kinase B/Akt, a prototypical downstream target of insulin signaling, develop severe NASH, progressive fibrosis, and eventual hepatocellular carcinoma [59], suggesting that certain insulin-initiated signals might actually promote (rather than prevent) liver damage. At this point, no unifying hypothesis has emerged to reconcile these seemingly contradictory results.

Efforts to equate DM with extremely severe insulin resistance contribute to the confusion. The flaw in such logic is demonstrated by recent data from the Diabetes Prevention Program (DPP). In that large population of insulin-resistant adults, hyposecretion of insulin was a better predictor of subsequent DM than the initial severity of insulin resistance [60]. This finding led the DPP investigators to speculate that insulin resistance “unmasked” individuals who have an inherently reduced capacity for pancreatic beta cell hyperplasia. The latter individuals eventually became overtly diabetic. This insight raises the intriguing possibility that cirrhosis, which strongly correlates with DM, might result from an inadequate hepatic hyperplastic response to similar metabolic stress. The latter is a particularly attractive concept because hepatocyte hyperplasia is necessary to replace dying fatty hepatocytes, and progressive liver damage results when regeneration cannot keep pace with injury.

Furthermore, situations that increase TNFα relative to adiponectin promote hepatic steatosis and insulin resistance [49]. TNFα also increases mitochondrial generation of reactive oxygen species (ROS), promotes hepatocyte apoptosis, and recruits inflammatory cells to the liver. Hence, protracted exposure to TNFα generates oxidative and apoptotic stress that sometimes overwhelms antioxidant and antiapoptotic defenses, leading to steatohepatitis [61]. Studies in mouse models of NASH, as well as mice who have ethanol-induced steatohepatitis, prove that over-production of TNFα relative
to adiponectin causes steatohepatitis, because treatments that inhibit TNFα or that increase adiponectin improve steatohepatitis in all of these models [48]. In addition, studies in humans who have NASH demonstrate that the relative risk of developing steatohepatitis correlates with increases in TNFα or decreases in adiponectin levels [62].

Given strong experimental and clinical evidence that unopposed TNFα activity promotes steatosis and steatohepatitis, it is interesting that there is now compelling evidence that the simple accumulation of fatty acids within hepatocytes is sufficient to trigger these cells to produce TNFα [63]. Fatty acids induce signaling in hepatocytes that activates kinases, such as inhibitor kappa kinase (IKK) beta that, in turn, activate the nuclear factor-kappa B (NF-κB) transcription factor, driving hepatocyte synthesis of TNFα and interleukin (IL)-6 [63,64]. Recent studies in transgenic mice who have hepatocyte-specific overexpression of IKK-beta demonstrate that hepatocyte-derived IL-6 is responsible for systemic insulin-resistance [64]. Therefore, like adipose tissue, fatty livers (and specifically, fatty hepatocytes) also make soluble factors that circulate to distant tissues and contribute to systemic insulin resistance (ie, the metabolic syndrome). These mechanisms of liver injury are likely similar in obese and nonobese individuals who develop NASH [65]. In support of this concept, recent data suggest that gut bacteria of some nonobese individuals might promote excessive hepatic accumulation of fatty acids, as well as exposure to other bacterial factors (eg, lipopolysaccharide or other Toll-like receptor agonists) that trigger hepatic TNFα production. As in obese individuals, increased TNFα would antagonize adiponectin activity, and promote steatosis, steatohepatitis, and insulin resistance [66].

It is generally believed that progression from fatty liver disease to cirrhosis is predominantly dictated by the severity of oxidant stress and consequent necroinflammation that occurs in individuals who have steatohepatitis [67,68]; however, findings in animal models of steatohepatitis cast some doubt on this assumption, because mice that develop severe steatohepatitis do not uniformly progress to cirrhosis [69]. In fact, progression to cirrhosis is also poorly predicted by the gravity of the injurious insult in human fatty liver disease. For example, although there is no doubt that alcohol is hepatotoxic, most lifelong heavy drinkers do not become cirrhotic [70]. Similarly, although obesity clearly increases exposure to fat-derived inflammatory mediators, some morbidly obese individuals have normal livers at the time of gastric bypass surgery [71].

These apparent paradoxes might be explained by the failure to acknowledge that liver damage is determined by the adequacy of liver repair mechanisms as well as the severity of a particular noxious insult. Individuals who are “poor repairers” suffer more net liver damage for any given level of injury than those who are “average repairers,” whereas those who are “super repairers” may survive relatively unscathed, with little evidence of liver damage despite a significant noxious exposure. Viewed from this perspective,
individuals who merely develop steatosis despite constant bombardment with inflammatory factors might be “super repairers,” whereas those who develop steatohepatitis have only “average” repair capabilities, and the minority who have “poor” repair abilities develop cirrhosis.

Indeed, the possibility that differences in repair responses might contribute to liver disease outcome merits consideration in fatty liver disease because this condition is often associated with obesity, and adipose tissue is an important source of various mediators that modulate wound-healing responses [49–51]. Indeed, hepatic stellate cells (HSC) express receptors for several of the adipose-derived factors that modulate HSC activation, including leptin, angiotensin, adiponectin, and norepinephrine [72]. Studies in mice demonstrate that leptin, angiotensin, and norepinephrine promote HSC proliferation, up-regulate HSC expression of pro-fibrogenic cytokines such as transforming growth factor-beta (TGF-β), and induce collagen gene expression [72,73]. Conversely, adiponectin appears to inhibit HSC activation and decrease liver fibrosis [74]. It is likely that plasminogen activator inhibitor 1 (PAI-1) also regulates HSC because it has been shown to influence fibrosis in other tissues [75].

In summary, studies of animal models and patients who have fatty liver disease suggest that the early-intermediate stages of this condition (ie, steatosis and steatohepatitis) are caused by excessive exposure to fatty acids and inflammatory cytokines that induce hepatocyte steatosis, threaten hepatocyte viability, and promote hepatic and systemic insulin resistance. Resultant increases in the rate of liver cell death trigger repair responses. The latter are modulated by various factors that regulate the activation of hepatic stellate cells. In some individuals, the net effect of this process is “unhealthy” repair, with resultant cirrhosis. More research is needed to clarify the molecular basis for inter-individual differences in repair responses that are triggered by chronic fatty liver injury. Improved understanding of such pathobiology should enhance identification of individuals who are at greatest risk for developing cirrhosis, as well as the development of effective treatments to abort disease progression.

**Potential management strategies**

The objective of treating NAFLD is to prevent disease progression and long-term complications related to cirrhosis. No practice guidelines for the management of NAFLD currently exist; however, flexible management strategies that may be tailored to specific patient circumstances are proposed. Specific recommendations are based on relevant and published information. Circumstances in which evidence-based literature does not provide data are also be specified.

**General considerations**

NAFLD should be considered in any patient who presents with abnormal liver enzymes or hepatomegaly, who is incidentally noted to have
a “bright” liver on sonogram, or who has any features of the metabolic syndrome. Initially, it is important to consider and exclude other causes of chronic liver disease, because NAFLD may coexist with other conditions that may require alternative therapies (i.e., hepatitis C virus [HCV] infection). Whether alcohol use should be completely prohibited or diminished to levels less than 20 g/day, both to define the existence of NAFLD and for counseling of patients, remains unclear. For now, physicians need to tailor recommendations regarding minimal alcohol consumption to individual patients depending on patient interview and associated liver histology. Because liver enzymes are not a sensitive measure for the presence of significant liver disease, even patients who have normal liver enzymes can have evidence of NASH or cirrhosis [39]. Therefore, liver biopsy, which remains the “gold-standard” for resolution of histologic abnormalities, should be considered in those persons at risk for fibrosis. In the future, magnetic resonance spectroscopy may prove to be the optimal means of quantifying visceral and periphery adiposity. A schematic diagram of a proposed therapeutic approach is outlined in Fig. 3.

Weight management

Diet and exercise continue to be the cornerstone of therapeutic interventions. Because obesity consistently has been associated with NAFLD, weight reduction has been one of the initial forms of treatment interventions. Medical interventions include diet and exercise, but preferably a combination of the

---

**Approach to Treatment of NAFLD**

- **Overt Features of Metabolic Syndrome**
  - Present
    - Treat and counsel regarding management of the clinical complications of IRS (e.g., DM, HTN, Hyperlipidemia, Obesity)
  - Absent
    - Glucose < 140 mg/dl
    - Glucose > 140 mg/dl
      - Treat IGC or DM

- **Treat NAFLD and Monitor for Disease Progression**
  - Steatosis
    - Diet / exercise, Weight loss
  - Steatohepatitis
    - Enroll into Clinical Trials
  - Cirrhosis
    - Treat & screen for portal HTN, HCC; Early referral for OLT

---

Fig. 3. Approach to treatment of NAFLD. IGC, impaired glycemic control; HTN, hypertension; HCC, hepatocellular carcinoma.
two. Most of the studies have suggested that weight loss can be associated with biochemical improvement [76–78]. Rarely, rapid weight loss may be associated with worsening inflammation [79]. Patients who are overweight (body mass index > 25 kg/m²) and have NAFLD should be considered for a weight loss program. A target of 10% of baseline weight is often used as an initial goal of weight loss [80]; however, even attaining as little as a 3% decrease in weight may enhance glucose tolerance and improve post-exercise insulin sensitivity [81]. Weight loss should proceed at a rate of 1 to 2 pounds a week [82]. Dietary recommendations generally include both caloric restriction and a decrease in saturated fats as well as total fats to 30% or less of total calories [83,84]. Currently there are no data to support or refute the value of decreasing saturated fats and increasing the fiber content of diet on NAFLD. On the other hand, decreased carbohydrate consumption may decrease insulin secretion [85,86]. Diet modifications are usually accompanied by a recommendation to exercise regularly. Both intermittent as well as daily exercise can help achieve weight loss and improve insulin sensitivity, even in the physically fit and fat individual [87]. Routine exercise alters substrate use in skeletal muscle and improves insulin sensitivity [88–90]. Unfortunately, despite earnest efforts, only about one third of patients are effective in achieving target levels of exercise [91–93]. Obese persons may be even more resistant to weight loss [94,95]. Studies of diet and exercise therapy reveal improved biochemical parameters but variable changes in histology [77,79,96–98]. Further research is needed to substantiate the benefits of weight loss on hepatic histopathology.

For patients who have a body mass index greater than 35 kg/m² and NAFLD, more aggressive weight management, such as bariatric surgery, should be considered in individuals who do not have evidence of portal hypertension. The current bariatric surgical procedures can be divided into two categories: restrictive or malabsorptive surgeries. Restrictive surgeries (ie, vertical banded gastroplasty or laproscopic gastric band procedures) decrease the capacity of the stomach and the amount of food consumption. Malabsorptive surgeries (ie, Roux-en-Y gastric bypass) bypass a large portion of small intestine, thus preventing absorption of fats and nutrients. The decision to perform this surgery should take into consideration the morbidity and mortality associated with the procedure, as well as the risk of developing subacute nonalcoholic steatohepatitis and liver failure during rapid weight loss; however, several studies have reported beneficial effects of bariatric surgery, with improvements in diabetes, hyperlipidemia, and hypertension [99], as well as steatosis and NASH [100]. Whether bariatric surgery also improves [101–103] or worsens fibrosis [97,104] remains unclear.

**Insulin sensitizing agents for the treatment of nonalcoholic fatty liver disease**

Current pharmacologic treatment approaches are guided by knowledge of NAFLD pathogenesis. To date, treatment approaches have been tailored
to improving hepatic insulin resistance or inhibiting the inflammatory response responsible for chronic hepatitis. Multiple pharmacologic agents have been tested for the treatment of NASH. Insulin-sensitizing agents are particularly attractive therapeutic agents for NASH because they improve peripheral and hepatic insulin resistance (Table 1). Metformin, a biguanide antihyperglycemic agent, has been evaluated in animals as well as patients who have NAFLD. In animal models of fatty liver, metformin improved hepatic steatosis and decreased hepatic tumor necrosis factor (TNF) and lipogenic transcription factors [105]. Several small pilot studies of up to 6 months duration using metformin at doses of 1.0 to 1.5 g/day have shown improvement in ALT levels compared with baseline [106–108]. Other pilot studies, using metformin doses of 1.5 to 2.0 g/day noted improvement in liver biochemistry, improved insulin resistance, and decreased echogenicity of the liver by ultrasound imaging [109], however, change in liver histology was variable [110,111].

The thiazolidinediones are promising therapies for NASH because these peroxisome proliferator-activated receptor (PPARγ) agonists inhibit inflammation, alter skeletal muscle glucose uptake, decrease central adiposity, promote adipocyte differentiation, and alter mitochondrial mass and thermogenesis. PPARγ agonists are also attractive therapeutic agents because of their anti-fibrotic properties. Troglitazone showed promising results in a pilot trial before being removed from the market because of idiosyncratic liver toxicity [112]. Although the PPARγ agonists appear to be safer, they are not currently US Food and Drug Administration (FDA)-approved for use in patients who have chronic liver disease. Two well-designed pilot studies using rosiglitazone (4 mg twice daily) [113] and pioglitazone (30 mg daily) [114] showed improvement in liver aminotransferases, radiologic, or histologic endpoints [114–116]. Pioglitazone, but not rosiglitazone, was associated with improvement in the overall fibrosis stage. A randomized trial of 20 nondiabetic patients who had NASH comparing pioglitazone (30 mg daily) plus vitamin E (400 IU daily) with vitamin E (400 IU daily) alone, found that both groups improved hepatic steatosis grade, although the improvement was greater with pioglitazone [115]; however, two thirds of patients experienced weight gain and the biochemical improvement reversed after discontinuation of treatment. Interpretation of these studies without a placebo group is difficult because ALT levels, hepatic steatosis, and inflammation on liver biopsy are insensitive measures of disease activity, and may improve over time as fibrosis progresses. In a recent placebo-controlled trial that compared diet plus pioglitazone (n = 26) with diet plus placebo (n = 21), pioglitazone improved glycemic control and glucose tolerance (P < .001), normalized liver aminotransferase levels as it decreased plasma AST levels (40% versus 21%, P = .04), decreased ALT levels (58% versus 34%, P < .001), decreased hepatic fat content (54% versus 0%, P < .001), and increased hepatic insulin sensitivity (48% versus 14%, P = .008) [116]. Administration of pioglitazone improved the histologic features of steatosis (P = .003), ballooning necrosis
<table>
<thead>
<tr>
<th>Reference</th>
<th>Therapy</th>
<th>N</th>
<th>Study type</th>
<th>Duration</th>
<th>Liver biochemistry</th>
<th>Liver histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marchesini et al [106]</td>
<td>Metformin</td>
<td>14</td>
<td>Open label</td>
<td>4 mo</td>
<td>Improved</td>
<td>NA</td>
</tr>
<tr>
<td>Magalotti et al [107]</td>
<td>Metformin</td>
<td>11</td>
<td>Open label</td>
<td>6 mo</td>
<td>Improved</td>
<td>NA</td>
</tr>
<tr>
<td>Schwimmer et al [108]</td>
<td>Metformin</td>
<td>10</td>
<td>Open label</td>
<td>6 mo</td>
<td>Improved</td>
<td>NA</td>
</tr>
<tr>
<td>Uygun et al [109]</td>
<td>Metformin</td>
<td>34</td>
<td>RCT, open label</td>
<td>6 mo</td>
<td>Improved</td>
<td>Improved (S)</td>
</tr>
<tr>
<td>Nair et al [110]</td>
<td>Metformin</td>
<td>15</td>
<td>Open label</td>
<td>12 mo</td>
<td>Improved</td>
<td>Variable</td>
</tr>
<tr>
<td>Bugiansi et al [111]</td>
<td>Metformin versus vit E versus diet</td>
<td>55a</td>
<td>Open label, randomized</td>
<td>12 mo</td>
<td>Improved</td>
<td>Improved (S, I, F)</td>
</tr>
<tr>
<td>Caldwell et al [112]</td>
<td>Troglitazone</td>
<td>10</td>
<td>Open label</td>
<td>≤ 6 mo</td>
<td>Improved</td>
<td>Improved (I)</td>
</tr>
<tr>
<td>Neushwander-Tetri et al [113]</td>
<td>Rosiglitazone</td>
<td>30</td>
<td>Open label</td>
<td>48 wk</td>
<td>Improved</td>
<td>Improved (I, F)</td>
</tr>
<tr>
<td>Promet et al [114]</td>
<td>Pioglitazone</td>
<td>18</td>
<td>Open label</td>
<td>12 mo</td>
<td>Improved</td>
<td>Improved (S, I, F)</td>
</tr>
<tr>
<td>Bajaj et al [125]</td>
<td>Pioglitazone</td>
<td>11</td>
<td>Open label</td>
<td>4 mo</td>
<td>Not done</td>
<td>NA</td>
</tr>
<tr>
<td>Belfort et al [116]</td>
<td>Pioglitazone</td>
<td>26</td>
<td>RCT</td>
<td>12 mo</td>
<td>Improved</td>
<td>Improved (S, I)</td>
</tr>
<tr>
<td>Sanyal et al [115]</td>
<td>Vit E versus vit E + pioglitazone</td>
<td>21</td>
<td>RCT, open label</td>
<td>6 mo</td>
<td>Not reported</td>
<td>Pioglitazone improved (S, I)</td>
</tr>
</tbody>
</table>

This table is not a comprehensive list of all clinical studies in patients with NAFLD. But is only intended to reflect only those trials with > 10 adult patients, >4 months duration, and with histologic endpoints.

a 55 of 110 patients enrolled were assigned to metformin. Of these, 17 of 55 patients underwent biopsy to assess change in liver histology.
b Drug removed from the market because of idiosyncratic hepatotoxicity.

Abbreviations: F, fibrosis; I, inflammation; mo, months; NA, not available; RCT, randomized controlled trial; S, steatosis; Vit E, vitamin E; wk, weeks.

Soylak et al [117] 
Magalotti et al [107] 
Bugiansi et al [111] 
Caldwell et al [112] 
Neushwander-Tetri et al [113] 
Promeet et al [114] 
Bajaj et al [125] 
Belfort et al [116] 
Sanyal et al [115] 

**Table 1**

Insulin sensitizing agents in the treatment of NAFLD
The reduction in fibrosis, however, did not differ significantly from that in the placebo group [116]. Despite these promising results, potential hepatotoxicity in the setting of liver disease remains a concern. Large randomized placebo-controlled trials are currently underway to further evaluate these encouraging data.

Because hypertriglyceridemia and low high-density lipoprotein (HDL) cholesterol levels are a manifestation of insulin resistance, and occur commonly among patients who have NAFLD, several investigators have used lipid lowering agents (ie, statins, fibrates) to treat NAFLD (Table 2). Unfortunately, these agents have not had a proven benefit [117]. Two pilot studies using atorvastatin showed improvement in biochemical [118] and histologic parameters in a small sample of patients who had NAFLD [119,120]; however, other reports have suggested no significant histologic differences between controls and patients who had NAFLD using various statin drugs [121]. In any case, it does not appear that patients who have NAFLD are at increased risk of hepatotoxicity with use of these agents [122,123]. Two small studies have also examined the fenofibrates, one 12 month trial of clofibrate (2 g daily) [124] showed no improvement in liver enzymes or histology, whereas gemfibrozole (600 mg daily) [117] improved liver enzymes after 4 weeks compared with no treatment. The role of resin binding agents has not yet been investigated. Therefore, no recommendation about the safety or efficacy of lipid-lowering agents in the management of NAFLD can be made at this time.

The role of pharmacologic agents to induce weight loss or improve oxidant stress in patients who have NAFLD has not been well-studied. The role of antioxidants (eg, vitamin C, vitamin E, betaine, S-adenosylmethionine, and the like) in improving insulin resistance and the histologic features of NAFLD remains uncertain. Given the small sample size, the randomized, placebo-controlled trials that have been performed for NAFLD have not shown convincing evidence of histologic improvement. Therefore, before recommending these (or other) agents as generalized treatments for NAFLD, larger, prospective controlled trials are needed to confirm their safety, efficacy, and impact on the natural history of disease progression.

**Monitoring of patients who have nonalcoholic fatty liver disease**

Regardless of the treatment approach selected, all patients who have NAFLD merit routine follow-up to monitor for evidence of disease progression. Routine monitoring by liver enzymes alone is insufficient, given their lack of sensitivity for detecting inflammation or fibrosis. In addition, it may take several decades for a patient at risk for disease progression to develop complications of cirrhosis. In view of the insensitivity of existing noninvasive tests for detecting progression of fibrosis, a periodic (every 7–10 years) liver biopsy has been suggested for patients who have NAFLD, as for
patients who have other types chronic liver disease. Studies of noninvasive fibrosis biomarkers are ongoing to determine if they might be helpful in monitoring fibrosis progression/regression, obviating the need for repeat biopsy in some individuals.

Given the intimate association of NAFLD with insulin resistance, a biannual physical examination and blood work to monitor for complications of the metabolic syndrome should be considered. General surveillance, counseling, and early intervention to control weight gain, hyperglycemia, hyperlipidemia, and hyperuricemia are warranted. If a decline in liver function (eg, bilirubin, albumin, prothrombin time) or significant drop in platelet count (ie, marker of portal hypertension) is noted during follow-up, imaging of the abdomen should be performed to assess the liver contour and presence of splenomegaly, intra-abdominal varices or ascites. Once cirrhosis is diagnosed by imaging or liver biopsy, screening, prophylaxis, or management of varices, ascites, encephalopathy, and hepatocellular carcinoma is initiated. Assuming no contraindications exist, such complications warrant consideration of liver transplantation and early referral to a liver transplant center. In patients who have any form of chronic liver disease, most hepatologists elect to vaccinate patients against hepatitis A and B to protect the patient from superinfection and the associated risk of acute on chronic liver injury. Readers should familiarize themselves with the screening, prevention, and palliation of complications related to cirrhosis, because that discussion is beyond the scope of this article.

Summary

Largely because of epidemic obesity and diabetes, NAFLD is now acknowledged as the most common cause of chronic liver disease in the Western world. As such, physicians across all specialties will be confronted with the evaluation and management of liver disease as a complication of insulin resistance. It is clear that NAFLD leads to liver-related morbidity and
mortality in a subset of people; however, a better understanding of the natural history for NAFLD will permit better identification of those patients at risk for fibrosis progression. Although diagnosis and evaluation are relatively straightforward, many issues remain unresolved. Large series of well-characterized patients will need to be followed to better establish the natural history and to clearly define the associated morbidity and mortality caused by this chronic condition. Furthermore, noninvasive means of discerning risk factors for fibrosis progression will allow clinicians and investigators to select out patients at high risk for disease progression for more comprehensive diagnostic evaluations, follow-up, and treatment interventions. Currently, treatment is limited to weight loss, exercise, and treatment of individual features of the metabolic syndrome. Effective pharmacologic therapies to improve steatohepatitis are currently being investigated, and several promising agents are on the horizon.

References


[64] Arkan MC, Hevener AL, Greten FR, et al. IKK-beta links inflammation to obesity-
[68] Green RM. Hepatic metabolism and not simply the metabolic syndrome. Hepatology 2003;
38:14–7.
[70] Tsukamoto H, Gaal K, French SW. Insights into the pathogenesis of alcoholic liver necro-
morbidly obese patients after weight loss induced by bariatric surgery. Obes Surg 2005;
1041–3.
[75] Lijnen HR. Pleiotropic functions of plasminogen activator inhibitor-1. J Thromb Haemost
[77] Ueno T, Sugawara H, Suejak K, et al. Therapeutic effects of restricted diet and exercise in
[78] Brolin RE. Bariatric surgery and long-term control of morbid obesity. JAMA 2002;288:
2973–6.
[81] O’Leary VB, Marchetti CM, Krishnan RK, et al. Exercise-induced reversal of insulin resis-
tance in obese elderly is associated with reduced visceral fat. J Appl Physiol 2006;100(5):
1584–9.
[82] Anonymous. Executive summary of the clinical guidelines on the identification, evaluation,
[84] Minehira K, Tappy L. Dietary and lifestyle interventions in the management of the meta-
[86] Arora SK, McFarlane SI. The case for low carbohydrate diets in diabetes management.
[87] Niskanen L, Uusitupa M, Sarlund H, et al. The effects of weight loss on insulin sensitivity,
[89] Duncan GE, Perri MG, Theriaque DW, et al. Exercise training, without weight loss,
increases insulin sensitivity and postheparin plasma lipase activity in previously sedentary


[122] Nair S, Wiseman M. HMG-CoA reductase inhibitors in nonalcoholic fatty liver disease: is potential hepatotoxicity an issue in these patients? A case-control study based on histology [Abstract]. Hepatology 2002;36:409A.

