Epidemiology, clinical features, and diagnosis of nonalcoholic fatty liver disease in adults

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) refers to the presence of hepatic steatosis when no other causes for secondary hepatic fat accumulation (eg, heavy alcohol consumption) are present. NAFLD may progress to cirrhosis and is likely an important cause of cryptogenic cirrhosis [1-4].

This topic will review the epidemiology, clinical features, and diagnosis of NAFLD. The pathogenesis, natural history, and treatment of NAFLD are discussed separately. (See "Pathogenesis of nonalcoholic fatty liver disease" and "Management of nonalcoholic fatty liver disease in adults".)

DEFINITIONS

Patients with nonalcoholic fatty liver disease (NAFLD) have hepatic steatosis, with or without inflammation and fibrosis. In addition, no secondary causes of hepatic steatosis are present. (See 'Differential diagnosis' below.)

NAFLD is subdivided into nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH). In NAFL, hepatic steatosis is present without evidence of significant inflammation, whereas in NASH, hepatic steatosis is associated with hepatic inflammation that may be

histologically indistinguishable from alcoholic steatohepatitis [5,6]. Other terms that have been used to describe NASH include pseudoalcoholic hepatitis, alcohol-like hepatitis, fatty liver hepatitis, steatonecrosis, and diabetic hepatitis. (See 'Histologic findings' below and 'NAFLD activity score' below.)

EPIDEMIOLOGY

Prevalence — Nonalcoholic fatty liver disease (NAFLD) is seen worldwide and is the most common liver disorder in Western industrialized countries, where the major risk factors for NAFLD, central obesity, type 2 diabetes mellitus, dyslipidemia, and metabolic syndrome are common [7]. In the United States, studies report a prevalence of NAFLD of 10 to 46 percent, with most biopsy-based studies reporting a prevalence of NASH of 3 to 5 percent [8-10]. Worldwide, NAFLD has a reported prevalence of 6 to 35 percent (median 20 percent).

- In a prospective study of 400 US military personnel and their families (mean age 55 years), the prevalence of NAFLD by ultrasound was 46 percent [8]. Factors associated with NAFLD included male sex, increasing age, and the presence of systemic hypertension, obesity, or diabetes.

- In a population-based sample that included 2133 subjects from the US who reported moderate or no alcohol intake, hepatic steatosis was present in 30 and 32 percent, respectively [11].

- Estimates of prevalence of NAFLD in Asia-Pacific regions range from 5 to 30 percent, depending upon the population studied [12].

In the US, the prevalence of NAFLD has been increasing over time. This increase was demonstrated in a comparison of three cycles of the National Health and Nutrition Examination Survey (NHANES):

- Between 1988 and 1994, the prevalence of NAFLD was 5.5 percent, between 1999 and 2004 it was 9.8 percent, and between 2005 and 2008 it was 11 percent, accounting for 47, 63, and 75 percent of chronic liver disease during those time periods, respectively [7].

  Over the same three time periods, there were also increases in the rates of other components of the metabolic syndrome (table 1), including obesity (22, 30, and 33 percent, respectively), type 2 diabetes (6, 8, and 9 percent, respectively), and systemic hypertension (23, 33, and 34 percent, respectively) [7]. (See "Metabolic syndrome (insulin resistance syndrome or syndrome X)".)

Of note, the definition of NAFLD used in the NHANES study (elevated serum aminotransferase levels in the absence of an alternative explanation) could lead to misclassification and likely underestimated the true prevalence of NAFLD, since patients with NAFLD may have normal serum aminotransferases. This is supported by the findings from a subsequent study from NHANES that used ultrasound data collected from patients between 1988 and 1994 [10]. In that study, the age-adjusted prevalence of NAFLD was estimated to be 19 percent. A third study that used a fatty liver index estimated that the prevalence of NAFLD between 2011 and 2012 was 30 percent [13]. The fatty liver index was derived to predict ultrasound-diagnosed fatty liver and took into account fasting insulin and triglyceride concentrations, body mass index, sex, and gamma-glutamyl transferase activity.

Patient demographics — Most patients are diagnosed with NAFLD in their 40s or 50s [14]. Studies vary with regard to the sex distribution of NAFLD, with some suggesting it is more common in women [5,15-21] and others suggesting it is more common in men [8,11,22-25].

There appear to be ethnic differences in the prevalence of NASH [8,11,26]. A study of hepatic triglyceride content in 2287 subjects from a US multiethnic, population-based sample found a higher prevalence of hepatic steatosis in Hispanic Americans (45 percent) compared with White (33 percent) or Black Americans (24 percent) [11]. The higher prevalence in Hispanic Americans was explained by a greater prevalence of obesity, although the lower prevalence in Black Americans persisted after controlling for body mass index and insulin sensitivity.

Association with other disorders — Patients with NAFLD (particularly those with NASH) often have one or more components of the metabolic syndrome (table 1) [5,15-17,22,24,27-34]. (See "Metabolic syndrome (insulin resistance syndrome or syndrome X)".):

- Obesity
- Systemic hypertension
- Dyslipidemia
- Insulin resistance or overt diabetes

This association was demonstrated in a study of 304 patients with NAFLD but without overt diabetes [24]. Liver biopsies were performed in 163 patients and revealed NASH in 120 (74 percent). Metabolic syndrome was seen in 53 percent of patients who did not undergo biopsy, in 67 percent of those with simple steatosis (NAFL) on biopsy, and in 88 percent of those with NASH on biopsy. After correcting for age, sex, and body mass index, metabolic syndrome was associated with an increased risk of severe fibrosis (odds ratio [OR] 3.5, 95% confidence interval [CI] 1.1-11.2).

While the metabolic syndrome is a known risk factor for cardiovascular disease and is common in patients with NAFLD, NAFLD may be independently associated with cardiovascular disease. In a study using data from NHANES, NAFLD was associated with cardiovascular disease after controlling for older age, male sex, obesity, type 2 diabetes, smoking, and family history of early myocardial infarction (OR 1.23; 95% CI 1.04-1.44) [35]. However, the study did not control for dyslipidemia or systemic hypertension, which could act as confounders, since hyperlipidemia is associated with both NAFLD and cardiovascular disease.

There are also data that suggest NAFLD is associated with cholecystectomy. This was examined using a group of 12,232 participants in a population-based survey from the United States [36]. After controlling for factors such as age, sex, body mass index, diabetes, and cholesterol levels, patients who underwent cholecystectomy were more than twice as likely to have NAFLD than those who had not undergone cholecystectomy (OR 2.4, 95% CI 1.8-3.3) [36]. An increased prevalence of NAFLD was not seen in patients with gallstones who had not undergone cholecystectomy.

Other conditions that have been associated with NAFLD, independent of their associations with obesity, include polycystic ovary syndrome, hypothyroidism, obstructive sleep apnea, hypopituitarism, and hypogonadism [37,38].

PATHOGENESIS

The pathogenesis of nonalcoholic fatty liver disease has not been fully elucidated. The most widely supported theory implicates insulin resistance as the key mechanism leading to hepatic steatosis, and perhaps also to steatohepatitis. Others have proposed that a "second hit", or additional oxidative injury, is required to manifest the necroinflammatory component of steatohepatitis. Hepatic iron, leptin, antioxidant deficiencies, and intestinal bacteria have all been suggested as potential oxidative stressors.

Genome-wide association studies have identified genetic variants associated with risk of progression from fatty liver to fibrosing NASH via effects on hepatic fat accumulation [39,40]. Predisposing genetic variants associated with progressive disease include *PNPLA3* and *IFNL4*, and their phenotypic expression is triggered by factors such as adiposity and dietary factors [39]. The pathogenesis of NAFLD is discussed in more detail separately. (See "Pathogenesis of nonalcoholic fatty liver disease".)

CLINICAL MANIFESTATIONS

Most patients with nonalcoholic fatty liver disease (NAFLD) are asymptomatic, although some patients with nonalcoholic steatohepatitis (NASH) may complain of fatigue, malaise, and vague right upper abdominal discomfort [22]. Patients are more likely to come to attention because laboratory testing revealed elevated liver aminotransferases or hepatic steatosis was detected incidentally on abdominal imaging.

Physical findings — Patients with NAFLD may have hepatomegaly on physical examination due to fatty infiltration of the liver [5,15,18,19,41]. In some patients, hepatomegaly is the presenting sign of NAFLD. The reported prevalence of hepatomegaly in patients with NAFLD is highly variable:

- In a population-based study of 1168 participants from Mumbai, NAFLD was detected on ultrasound in 19 percent of those older than 20 years of age [41]. Among those with NAFLD, 5 percent had hepatomegaly.

- In a study of 12 patients with NASH who underwent computed tomography (CT) scanning, 11 had hepatomegaly (defined as a liver span of >18 cm), with a mean liver span for all 12 of 21 cm [42].

- In a study of 144 patients with NASH, 18 percent were noted to have hepatomegaly on examination and/or ultrasound, and there was a trend toward an increased rate of hepatomegaly among those with more advanced fibrosis (28 percent) [18].

The population-based study likely provides a better estimate of the prevalence of hepatomegaly in patients with NAFLD since it does not subject to referral bias. However, the study did not differentiate between patients with nonalcoholic fatty liver and those with NASH, and as suggested by the third study, it is possible that hepatomegaly is more prevalent in patients with more advanced disease.

Patients who have developed cirrhosis may have stigmata of chronic liver disease (eg, palmar erythema, spider angiomata, ascites). (See "Cirrhosis in adults: Etiologies, clinical manifestations, and diagnosis", section on 'Clinical manifestations'.)

Laboratory findings — Patients with NAFLD may have mild or moderate elevations in the aspartate aminotransferase (AST) and alanine aminotransferase (ALT) [22], although normal aminotransferase levels do not exclude NAFLD [43-45]. The true prevalence of abnormal transaminases among patients with NAFLD is unclear, since many patients with NAFLD are diagnosed because they are noted to have abnormal aminotransferases. When elevated, the AST and ALT are typically two to five times the upper limit of normal, with an AST to ALT ratio of less than one (unlike alcoholic fatty liver disease, which typically has a ratio greater than two)

[14,46-48]. The degree of aminotransferase elevation does not predict the degree of hepatic inflammation or fibrosis, and a normal alanine aminotransferase does not exclude clinically important histologic injury [22,32,43]. (See 'Significant alcohol consumption' below and "Clinical manifestations and diagnosis of alcohol-associated fatty liver disease and cirrhosis".)

The alkaline phosphatase may be elevated to two to three times the upper limit of normal. Serum albumin and bilirubin levels are typically within the normal range, but may be abnormal in patients who have developed cirrhosis. Other laboratory abnormalities that may be seen in patients who have developed cirrhosis include a prolonged prothrombin time, thrombocytopenia, and neutropenia. (See "Cirrhosis in adults: Etiologies, clinical manifestations, and diagnosis", section on 'Laboratory findings'.)

Patients with NAFLD may have an elevated serum ferritin concentration or transferrin saturation [18,22]. There is evidence that a serum ferritin greater than 1.5 times the upper limit of normal in patients with NAFLD is associated with a higher nonalcoholic fatty liver disease activity score (and thus, NASH) and with advanced hepatic fibrosis [49]. Patients with NAFLD may also have positive serum autoantibodies (antinuclear antibody, antismooth muscle antibody), though the significance of these findings is unclear [37]. (See 'NAFLD activity score' below.)

Radiographic findings — Radiographic findings in patients with NAFLD include increased echogenicity on ultrasound, decreased hepatic attenuation on CT, and an increased fat signal on magnetic resonance imaging (MRI). (See 'Radiographic examinations' below.)

Associated disorders — In addition to the findings related to NAFLD, patients often have findings associated with the metabolic syndrome (table 1). (See 'Association with other disorders' above and "Metabolic syndrome (insulin resistance syndrome or syndrome X)".)

DIAGNOSIS

The diagnosis of nonalcoholic fatty liver disease (NAFLD) requires all of the following [37]:

- Demonstration of hepatic steatosis by imaging or biopsy
- Exclusion of significant alcohol consumption
- Exclusion of other causes of hepatic steatosis
- Absence of coexisting chronic liver disease

In those undergoing a radiologic evaluation, radiologic findings are often sufficient to make the diagnosis if other causes of hepatic steatosis have been excluded. While not indicated for the

majority of patients, a liver biopsy may be indicated if the diagnosis is not clear or to assess the degree of hepatic injury. In addition, liver biopsy is the only method currently available to differentiate nonalcoholic fatty liver (NAFL) from nonalcoholic steatohepatitis (NASH). (See 'Differential diagnosis' below and 'Role of liver biopsy' below.)

Laboratory tests — Laboratory tests, such as the serum aminotransferase and ferritin levels, are often abnormal in NAFLD. However, these abnormalities are neither required nor sufficient for making the diagnosis, as laboratory tests may be normal in patients with NAFLD and may be abnormal in patients with numerous other conditions. (See 'Laboratory findings' above and 'Differential diagnosis' below.)

However, laboratory testing is required to evaluate for other conditions in the differential diagnosis of hepatic steatosis.

Rule out other disorders — Differentiating NAFLD from the other items in the differential diagnosis begins with a thorough history to identify potential causes such as significant alcohol use, starvation, medication use, and pregnancy-related hepatic steatosis. (See "Clinical manifestations and diagnosis of alcohol-associated fatty liver disease and cirrhosis".)

We test all patients with hepatic steatosis for hepatitis C virus infection. We also test for hepatitis A and B. We do this to both to rule out these infections in patients with elevated aminotransferases and to determine immunity to guide future immunizations. We also rule out other chronic liver diseases such as autoimmune hepatitis and hemochromatosis. (See "Hepatitis A virus infection in adults: Epidemiology, clinical manifestations, and diagnosis", section on 'Diagnosis' and "Hepatitis B virus: Screening and diagnosis in adults" and "Immunizations for adults with chronic liver disease" and "Screening and diagnosis of chronic hepatitis C virus infection".)

We obtain the following tests in all patients:

- Anti-hepatitis C virus antibody.
- Hepatitis A IgG.
- Hepatitis B surface antigen, surface antibody, and core antibody.
- Plasma iron, ferritin, and total iron binding capacity.
- Serum gammaglobulin level, antinuclear antibody, antismooth muscle antibody, and anti-liver/kidney microsomal antibody-1 (see "Overview of autoimmune hepatitis", section on 'Diagnostic evaluation').

Other disorders that should be considered based upon the patient's history, associated symptoms, and family history include Wilson disease, thyroid disorders, celiac disease, alpha-1

antitrypsin deficiency, HELLP, and Budd-Chiari syndrome. (See "Approach to the patient with abnormal liver biochemical and function tests", section on 'Elevated serum aminotransferases'.)

Radiographic examinations — Various radiologic methods can detect NAFLD, but no imaging modality is routinely used to differentiate between the histologic subtypes of nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH) [50]. Our approach in patients who have not already undergone imaging is to obtain an ultrasound. However, computed tomography (CT) and magnetic resonance imaging (MRI) can also detect hepatic steatosis.

We consider a radiographic diagnosis to be sufficient for diagnosing NAFLD if all of the following conditions are met:

- Radiographic imaging is consistent with fatty infiltration.

- Other causes for the patient's liver disease have been excluded (see 'Differential diagnosis' below).

- The patient does not have signs or symptoms cirrhosis.

- The patient is not at high risk for advanced fibrosis or cirrhosis (eg, a younger patient who does not have diabetes and has a normal serum ferritin is at lower risk for having fibrosis or cirrhosis) (see "Management of nonalcoholic fatty liver disease in adults", section on 'Risk factors').

If these criteria are not met, patients will typically require a liver biopsy to make the diagnosis or to assess the degree of liver injury. (See 'Role of liver biopsy' below.)

Ultrasound — Ultrasonography often reveals a hyperechoic texture or a bright liver because of diffuse fatty infiltration [51]. A meta-analysis of 49 studies with 4720 patients found that the sensitivity and specificity for ultrasound were 85 and 94 percent, respectively, when using liver biopsy as the gold standard [52]. However, the sensitivity appears to be decreased in patients who are obese [53,54]. In a study of 187 patients with Class 2 obesity undergoing bariatric surgery, hepatic steatosis was present histologically in 95 percent but was only detected by ultrasound in 49 percent [53].

Vibration controlled transient elastography — Vibration controlled transient elastography, which is routinely used to grade fibrosis based on liver stiffness, is also being developed to grade hepatic steatosis [55-57]. However, additional data are needed to show how transient elastography measurements are reproducible, valid, and associated with clinical outcomes. In a meta-analysis of 19 biopsy-controlled studies including over 2700 patients, the optimal cutoff value for steatosis grade >S0 was 248 dB/m (95% CI 237-261) and for steatosis grade >S1 was

268 dB/m (95% CI 257-284) [56]. (See "Noninvasive assessment of hepatic fibrosis: Ultrasound-based elastography".)

CT, MRI, and magnetic resonance spectroscopy — Both CT and MRI can identify steatosis but are not sufficiently sensitive to detect inflammation or fibrosis [58]. Magnetic resonance spectroscopy (MRS) has the advantage of being quantitative rather than qualitative or semiquantitative, but it is not widely available [59].

One of the difficulties in determining the sensitivity and specificity of CT and MRI for diagnosis of hepatic steatosis is that not all patients undergo confirmation by liver biopsy. In a study that did use histology as the gold standard, the sensitivity of CT scan for detecting hepatic steatosis was poor, whereas MRI had low specificity [60]. It included a total of 131 patients who had a radiologic evaluation with noncontrast CT, contrast-enhanced CT, or MRI before undergoing a partial hepatectomy, usually for malignancy. The sensitivities of noncontrast CT, contrast-enhanced CT, and MRI for detecting hepatic steatosis were 33, 50, and 88 percent, respectively. The specificities were 100, 83, and 63 percent, respectively. In addition, the accuracy of noncontrast CT fell with increasing body mass index. However, in a study of 33 patients with diabetes at risk for NAFLD, the sensitivity and specificity of in-phase and out-of-phase MRI for hepatic steatosis were 95 and 98 percent, respectively [61].

Unlike CT and MRI, MRS allows for quantification of hepatic fat, and may be particularly helpful in patients with small amounts of hepatic steatosis [62]. A study that compared MRS with liver biopsy in 12 patients found a close correlation between the measurement of intrahepatocellular lipid by MRS and the histologic assessment of cirrhosis (r = 0.94) [63]. However, not all scanners have the capability of obtaining spectroscopic sequences, and it is not routinely used.

Role of liver biopsy — While liver biopsy is the gold standard for diagnosing NAFLD, in many cases a presumptive diagnosis can be made based upon the patient's history, laboratory tests, and imaging findings, provided other disorders have been excluded. However, some patients will continue to have an unclear diagnosis following a noninvasive evaluation. In such cases, a liver biopsy is indicated.

In addition, imaging studies and laboratory tests do not reliably differentiate patients with NAFL from those with NASH, or predict the severity of liver disease [64]. The only way to definitively confirm or exclude the diagnosis of NASH and to determine disease severity is with a liver biopsy [6,65]. This information can be used to guide patient care and may motivate patients to enact lifestyle modifications. As examples, patients found to have cirrhosis will require screening for esophageal varices and hepatocellular carcinoma, whereas patients with early fibrosis may be motivated to lose weight to decrease the risk of progressing to cirrhosis. (See

"Management of nonalcoholic fatty liver disease in adults", section on 'Management' and "Management of nonalcoholic fatty liver disease in adults", section on 'Monitoring for fibrosis'.)

A potentially useful non-invasive method for excluding advanced fibrosis is measurement of liver stiffness with transient elastography. However, the approach is not widely available and has not been extensively studied in NASH. Other indirect markers of cirrhosis such as the aspartate aminotransferase to platelet ratio index are also being studied to identify patients with fibrosis. (See "Noninvasive assessment of hepatic fibrosis: Overview of serologic tests and imaging examinations".)

Which patients to biopsy — There is no clear consensus about which patients require a liver biopsy [66]. We obtain a liver biopsy in patients with suspected NAFLD if the diagnosis is unclear after obtaining standard laboratory tests and hepatic imaging, if there is evidence of cirrhosis, if the patient wants to know if inflammation or fibrosis is present, or if the patient is at increased risk for advanced fibrosis or cirrhosis. (See 'Laboratory findings' above and "Cirrhosis in adults: Etiologies, clinical manifestations, and diagnosis", section on 'Clinical manifestations' and "Management of nonalcoholic fatty liver disease in adults", section on 'Risk factors'.)

Specifically, we obtain a biopsy if the patient:

- Has peripheral stigmata of chronic liver disease (suggestive of cirrhosis)
- Has splenomegaly (suggestive of cirrhosis)
- Has cytopenias (suggestive of cirrhosis)
- Has a serum ferritin >1.5 times the upper limit of normal (suggestive of NASH and advanced fibrosis)
- Is >45 years of age with associated obesity or diabetes (increased risk of advanced fibrosis)

Histologic findings — NAFLD is subdivided into nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH) although these are considered to be part of a spectrum. (See 'Definitions' above and "Histologic scoring systems for chronic liver disease".)

The minimum criterion for a histologic diagnosis of NAFLD is >5 percent steatotic hepatocytes in a liver tissue section [67,68]. In addition to steatosis, patients with NAFLD may also have hepatic iron deposition [69,70].

Nonalcoholic fatty liver can be distinguished from NASH based on histologic findings. NAFL is present when the liver biopsy shows any of the following [68]:

- Steatosis alone.
- Steatosis with lobular or portal inflammation, without hepatocyte ballooning.

- Steatosis with hepatocyte ballooning but without inflammation [71].

The histologic diagnosis of NASH requires the presence of hepatic steatosis in association with hepatocyte ballooning degeneration and hepatic lobular inflammation (typically in acinar zone 3) [68,71]. Fibrosis is not a required diagnostic feature, but may be seen. The appearance of NASH may be histologically indistinguishable from alcoholic steatohepatitis. (See "Alcoholic hepatitis: Clinical manifestations and diagnosis".)

Additional histologic findings of NASH include (picture 1A-C) [72-74]:

- Apoptotic (acidophil) bodies.

- Mild chronic portal inflammation (inflammation that is severe or is disproportionate to the acinar lesions is suggestive of concurrent hepatitis C).

- Perisinusoidal collagen deposition that may result in zone 3 accentuation in a "chicken wire" pattern (related to the deposition of collagen and other extracellular matrix fibers along the sinusoids of zone 3 and around hepatocytes).

- Portal fibrosis without perisinusoidal or pericellular fibrosis.

- Cirrhosis, which is typically macronodular or mixed.

- Mallory-Denk bodies (previously called Mallory bodies or Mallory's hyaline).

- Megamitochondria.

- Glycogenated (vacuolated) nuclei in periportal hepatocytes (rarely seen in alcoholic steatohepatitis).

- Lobular lipogranulomas.

- PAS-diastase-resistant Kupffer cells.

- Hepatic siderosis (typically mild) involving periportal hepatocytes or panacinar reticuloendothelial cells.

As fibrosis progresses to cirrhosis, steatosis and inflammation may not be reliably identified, resulting in a diagnosis of "cryptogenic" cirrhosis [74]. It is possible that portal fibrosis alone may represent a variant of NASH [75]. In biopsy specimens from children, portal inflammation may be more prominent than in adults [72].

NASH may exist concurrently with other liver diseases, though diagnosing NASH in that setting can be difficult. As an example, patients with NASH may also have alcoholic liver disease, but there is no way to differentiate the relative contributions of the two processes from a liver biopsy [74]. In a series of 3581 liver biopsies from patients with various chronic liver diseases, concurrent steatohepatitis was found in 5.5 percent of patients with hepatitis C (some with significant alcohol use) [76]. Among patients with other chronic liver diseases of nonalcoholic etiology, the prevalence ranged from 1.6 percent (autoimmune hepatitis) to 7.9 percent (alpha-1 antitrypsin deficiency). None of the patients with steatohepatitis with chronic liver disease from a cause other than hepatitis C had significant alcohol consumption.

NAFLD activity score — The NAFLD activity score (NAS) is a validated score that is used to grade disease activity in patients with NAFLD [77]. The NAS is the sum of the biopsy's individual scores for steatosis (0 to 3), lobular inflammation (0 to 3), hepatocellular ballooning (0 to 2). Fibrosis is not included in the NAS. In the original study that derived the NAS, scores of 0 to 2 occurred in cases largely considered not diagnostic of NASH; scores of 3 to 4 were evenly divided among those considered not diagnostic, borderline, or positive for NASH; and scores of 5 to 8 occurred in cases that were largely considered diagnostic of NASH. (See "Histologic scoring systems for chronic liver disease", section on 'Nonalcohol-associated fatty liver activity score'.)

Noninvasive assessment of hepatic fibrosis — There are now several noninvasive methods to detect fibrosis in patients with liver disease. One of the scores, the NAFLD fibrosis score, is specific to NAFLD. The score takes into account the patient's age, body mass index, hyperglycemia, aminotransferase levels, platelet count, and albumin. Studies suggest that higher NAFLD fibrosis scores may be associated with increased mortality from cardiovascular disease. (See "Noninvasive assessment of hepatic fibrosis: Overview of serologic tests and imaging examinations", section on 'Other indirect markers' and "Management of nonalcoholic fatty liver disease in adults".)

DIFFERENTIAL DIAGNOSIS

Alternative causes of hepatic steatosis — There are multiple causes of hepatic steatosis that should be considered in a patient with suspected nonalcoholic fatty liver disease (NAFLD). Causes of hepatic steatosis in addition to NAFLD include [37]:

- Alcoholic liver disease
- Hepatitis C (particularly genotype 3)
- Wilson disease

- Lipodystrophy
- Starvation
- Parenteral nutrition
- Abetalipoproteinemia
- Medications (amiodarone, methotrexate, tamoxifen, glucocorticoids, valproate, anti-retroviral agents for HIV)
- Reye syndrome
- Acute fatty liver of pregnancy
- HELLP (hemolytic anemia, elevated liver enzymes, low platelet count) syndrome
- Inborn errors of metabolism (LCAT deficiency, cholesterol ester storage disease, Wolman disease)
- Drug-induced liver disease

Significant alcohol consumption — Several definitions have been proposed for what constitutes significant alcohol consumption [78]. We define significant alcohol consumption as an average consumption of >21 standard drinks per week in men or >14 standard drinks per week in women over at least a two-year period, a definition that is consistent with a guideline from the American Association for the Study of Liver Diseases [37].

A standard alcoholic drink is any drink that contains about 14 grams of pure alcohol, according to the National Institute on Alcohol Abuse and Alcoholism (　figure 1) [79].

One finding that suggests alcoholic fatty liver disease rather than NAFLD is an aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio >2 (it is typically <1 in patients with NAFLD). The alcoholic liver disease to NAFLD index (ANI) is a model that has been developed to predict the probability that steatohepatitis is due to alcoholic liver disease [80]. The model is based upon aminotransferase levels, mean corpuscular volume (MCV), body mass index (BMI), and sex:

ANI = -58.5 + 0.637 (MCV) + 3.91 (AST/ALT) – 0.406 (BMI) + 6.35 for men

An ANI greater than zero favors a diagnosis of alcoholic liver disease, whereas an ANI less than zero favors a diagnosis of NAFLD. The probability of the patient having alcoholic liver disease rather than NAFLD is then calculated using the value obtained for the ANI:

Probability = $e^{ANI}/(1+e^{ANI})$

The ability of the model to accurately categorize patients ranged from good to excellent in validation cohorts [80].

SCREENING

One issue that arises is whether to screen patients for NAFLD if they are at increased risk because of an associated condition, such as diabetes or obesity. (See 'Association with other disorders' above.)

Society guidelines support screening for NAFLD-related fibrosis in selected, high-risk groups, and we agree with the recommendation to screen patients with type 2 diabetes using the Fibrosis (FIB)-4 index [81]. The FIB-4 index predicts advanced fibrosis by combining biochemical values (platelet count, ALT, and AST) and age (calculator 1 and calculator 2) [82]. Patients who have an intermediate or high risk for advanced fibrosis based on FIB-4 should be further evaluated with liver stiffness measurement (LSM) by elastography and referred to a liver specialist. (See "Noninvasive assessment of hepatic fibrosis: Overview of serologic tests and imaging examinations".)

For patients with a low-risk FIB-4 index, screening with the FIB-4 every one to three years is reasonable.

Observational data suggested that rates of hepatic steatosis in patients with type 2 diabetes were high [81,83-85]. In a study including 561 patients with type 2 diabetes who had noninvasive testing (eg, elastography, FIB-4) followed by liver biopsy if the results suggested fibrosis, the prevalence of steatosis and fibrosis (LSM ≥7 kPa) were 70 and 21 percent, respectively [84].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Nonalcoholic fatty liver disease".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more

sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Nonalcoholic fatty liver disease (The Basics)")

- Beyond the Basics topics (see "Patient education: Nonalcoholic fatty liver disease (NAFLD), including nonalcoholic steatohepatitis (NASH) (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Definitions** – Nonalcoholic fatty liver disease (NAFLD) refers to the presence of hepatic steatosis when no other causes for secondary hepatic fat accumulation (eg, heavy alcohol consumption (figure 1)) are present. NAFLD may progress to cirrhosis and is likely an important cause of cryptogenic cirrhosis. (See 'Definitions' above.)

  NAFLD is subdivided into nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH). In NAFL, hepatic steatosis is present without evidence of significant inflammation, whereas in NASH, hepatic steatosis is associated with hepatic inflammation that may be histologically indistinguishable from alcohol-associated steatohepatitis.

- **Clinical manifestations** – Most patients with NAFLD are asymptomatic, although some patients with NASH may complain of fatigue, malaise, and vague right upper abdominal discomfort. Patients are more likely to come to attention because laboratory testing revealed elevated liver aminotransferases or hepatic steatosis was detected incidentally on abdominal imaging. (See 'Clinical manifestations' above.)

  Patients with NAFLD may have mild or moderate elevations in the aspartate aminotransferase and alanine aminotransferase, although normal aminotransferase levels do not exclude NAFLD. (See 'Laboratory findings' above.)

  Radiographic findings in patients with NAFLD include increased echogenicity on ultrasound, decreased hepatic attenuation on computed tomography, or an increased fat signal on magnetic resonance imaging. (See 'Radiographic findings' above.)

- **Diagnosis** – A definitive diagnosis of NAFLD requires all of the following (see 'Diagnosis' above):

  - Demonstration of hepatic steatosis by imaging or biopsy
  - Exclusion of significant alcohol consumption
  - Exclusion of other causes of hepatic steatosis
  - Absence of coexisting chronic liver disease

  Radiologic findings are often sufficient to make a diagnosis of NAFLD, provided other causes of hepatic steatosis have been excluded. However, liver biopsy may be indicated if the diagnosis is not clear or to assess the degree of hepatic injury. (See 'Radiographic examinations' above and 'Role of liver biopsy' above.)

- **Differential diagnosis** – Other causes of hepatic steatosis include (see 'Differential diagnosis' above):

  - Significant alcohol use
  - Hepatitis C (particularly genotype 3)
  - Wilson disease
  - Lipodystrophy
  - Starvation
  - Parenteral nutrition
  - Abetalipoproteinemia
  - Medications
  - Reye syndrome
  - Acute fatty liver of pregnancy
  - HELLP (hemolytic anemia, elevated liver enzymes, low platelet count) syndrome
  - Inborn errors of metabolism

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Topic 3625 Version 51.0

GRAPHICS

Definitions of the metabolic syndrome

Parameters	NCEP ATP3 2005*	IDF 2009	EGIR 1999	WHO 1999	AACE 2003
Required			Insulin resistance or fasting hyperinsulinemia (ie, in top 25% of the laboratory-specific reference range)	Insulin resistance in top 25%$^\Delta$; fasting glucose ≥6.1 mmol/L (110 mg/dL); 2-hour glucose ≥7.8 mmol/L (140 mg/dL)	High risk of insulin resistance$^\diamond$ or BMI ≥25 kg/m^2 or waist ≥102 cm (men) or ≥88 cm (women)
Number of abnormalities	≥3 of:	≥3 of:	And ≥2 of:	And ≥2 of:	And ≥2 of:
Glucose	Fasting glucose ≥5.6 mmol/L (100 mg/dL) or drug treatment for elevated blood glucose	Fasting glucose ≥5.6 mmol/L (100 mg/dL) or diagnosed diabetes	Fasting glucose 6.1 to 6.9 mmol/L (110 to 125 mg/dL)		Fasting glucose ≥6.1 mmol/L (110 mg/dL); ≥2-hour glucose 7.8 mmol/L (140 mg/dL)
HDL cholesterol	<1.0 mmol/L (40 mg/dL) (men); <1.3 mmol/L (50 mg/dL) (women) or drug treatment for	<1.0 mmol/L (40 mg/dL) (men); <1.3 mmol/L (50 mg/dL) (women) or drug treatment	<1.0 mmol/L (40 mg/dL)	<0.9 mmol/L (35 mg/dL) (men); <1.0 mmol/L (40	<1.0 mmol/L (40 mg/dL) (men); <1.3 mmol/L (50

	low HDL cholesterol[§]	for low HDL cholesterol		mg/dL) (women)	mg/dL) (women)
Triglycerides	≥1.7 mmol/L (150 mg/dL) or drug treatment for elevated triglycerides[§]	≥1.7 mmol/L (150 mg/dL) or drug treatment for high triglycerides	or ≥2.0 mmol/L (180 mg/dL) or drug treatment for dyslipidemia	or ≥1.7 mmol/L (150 mg/dL)	≥1.7 mmol/L (150 mg/dL)
Obesity	Waist ≥102 cm (men) or ≥88 cm (women)[¥]	Waist ≥94 cm (men) or ≥80 cm (women)	Waist ≥94 cm (men) or ≥80 cm (women)	Waist/hip ratio >0.9 (men) or >0.85 (women) or BMI ≥30 kg/m^2	
Hypertension	≥130/85 mmHg or drug treatment for hypertension	≥130/85 mmHg or drug treatment for hypertension	≥140/90 mmHg or drug treatment for hypertension	≥140/90 mmHg	≥130/85 mmHg

NCEP: National Cholesterol Education Program; IDF: International Diabetes Federation; EGIR: Group for the Study of Insulin Resistance; WHO: World Health Organization; AACE: American Association of Clinical Endocrinologists; HDL: high-density lipoprotein; CVD: cardiovascular disease; BMI: body mass index.

* Most commonly agreed upon criteria for metabolic syndrome. Note that abdominal obesity is **not** a prerequisite for diagnosis; the presence of any 3 of the 5 risk criteria constitutes a diagnosis of metabolic syndrome.

¶ For South Asian and Chinese patients, waist ≥90 cm (men) or ≥80 cm (women); for Japanese patients, waist ≥90 cm (men) or ≥80 cm (women).

Δ Insulin resistance measured using insulin clamp.

◊ High risk of being insulin resistant is indicated by the presence of at least 1 of the following: diagnosis of CVD, hypertension, polycystic ovary syndrome, non-alcoholic fatty liver disease or acanthosis nigricans; family history of type 2 diabetes, hypertension or CVD; history of gestational diabetes or glucose intolerance; non-White race; sedentary lifestyle; BMI 25 kg/m^2 or waist circumference 94 cm (men) or 80 cm (women); and age 40 years.

§ Treatment with 1 or more of fibrates or niacin.

¥ In Asian patients, waist ≥90 cm (men) or ≥80 cm (women).

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Graphic 53446 Version 14.0

Nonalcoholic steatohepatitis on biopsy
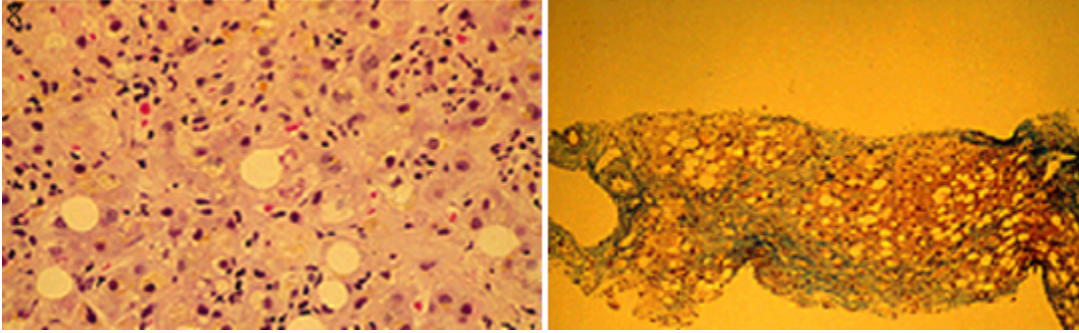
Histologic changes in nonalcoholic steatohepatitis (NASH). Left panel: The hepatocyte in the center contains a large vacuole of fat and deeply staining eosinophilic strands of cytoplasmic hyalin. Numerous neutrophils and phagocytic cells containing golden brown pigmented material (bile components and cellular debris) are present in the sinusoids. Right panel: NASH with cirrhosis. Trichrome stain shows regenerating nodules with fat surrounded by fibrous tissue.

Graphic 51497 Version 2.0

Nonalcoholic steatohepatitis liver biopsy
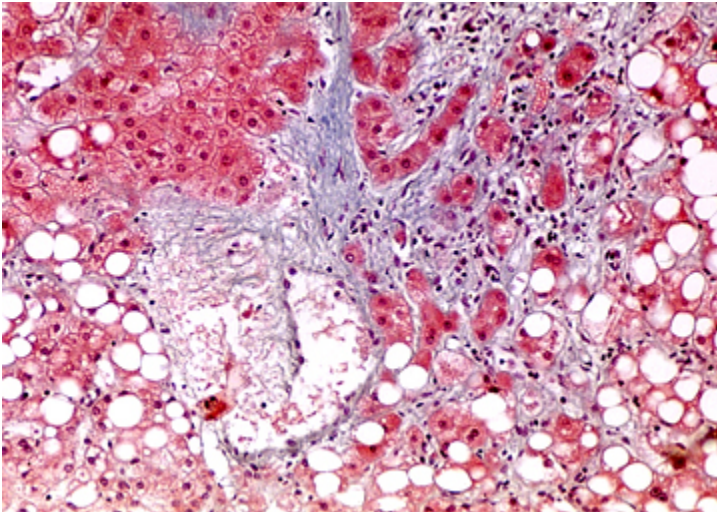
Liver biopsy showing steatosis, hepatocyte balloon degeneration, mixed acute and chronic inflammation, and pericellular fibrosis.

Courtesy of Marshall M. Kaplan, MD.

Graphic 59170 Version 1.0

Mallory-Denk bodies in alcoholic hepatitis
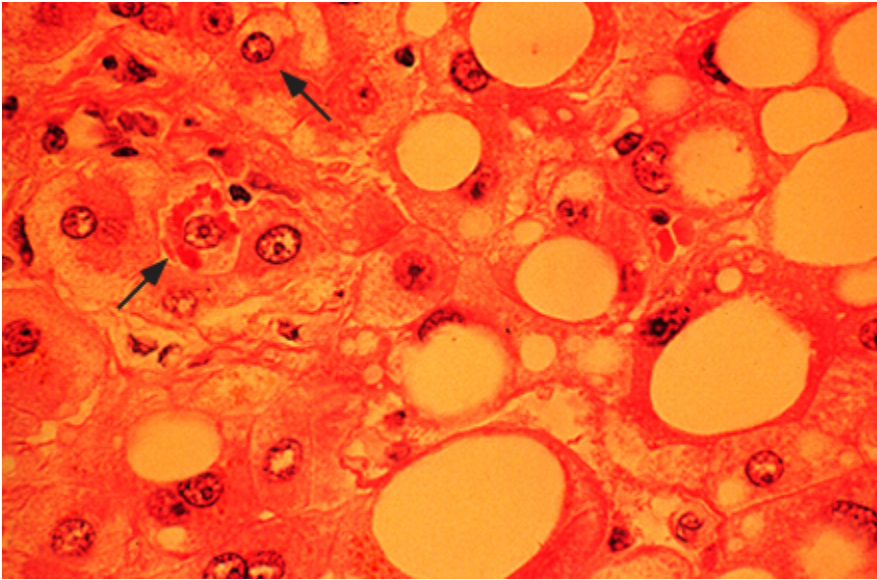
High power view of a liver biopsy in alcoholic hepatitis shows macrovesicular fat and Mallory-Denk bodies (arrows), which are eosinophilic accumulations of intracellular material. Similar changes can occur in nonalcoholic steatohepatitis.

Courtesy of Robert Odze, MD.

Graphic 75188 Version 3.0

What is a standard drink?

A standard drink in the United States is any drink that contains about 14 grams of pure alcohol (about 0.6 fluid ounces or 1.2 tablespoons). Below are US standard drink equivalents. These are approximate, since different brands and types of beverages vary in their actual alcohol content.

12 oz. of beer or cooler	8 to 9 oz. of malt liquor 8.5 oz. shown in a 12-oz. glass that, if full, would hold about 1.5 standard drinks of malt liquor	5 oz. of table wine	3 to 4 oz. of fortified wine (such as sherry or port) 3.5 oz. shown	2 to 3 oz. of cordial, liqueur, or aperitif 2.5 oz. shown	1.5 oz. of brandy (a single jigger)	1.5 oz. of spirits (a single jigger of 80-proof gin, vodka, whiskey, etc) Shown straight and in a highball glass with ice to show the level before adding a mixer*
~5% alcohol	~7% alcohol	~12% alcohol	~17% alcohol	~24% alcohol	~40% alcohol	~40% alcohol
12 oz.	8.5 oz.	5 oz.	3.5 oz.	2.5 oz.	1.5 oz.	1.5 oz.

Many people don't know what counts as a standard drink and so they don't realize how many standard drinks are in the containers in which these drinks are often sold. Some examples:

- For **beer**, the approximate number of standard drinks in:
  - 12 oz. = 1
  - 16 oz. = 1.3
  - 22 oz. = 2
  - 40 oz. = 3.3

- For **malt liquor**, the approximate number of standard drinks in:
  - 12 oz. = 1.5
  - 16 oz. = 2
  - 22 oz. = 2.5
  - 40 oz. = 4.5

- For **table wine**, the approximate number of standard drinks in:
  - a standard 750-mL (25-oz.) bottle = 5

- For **80-proof spirits**, or "hard liquor," the approximate number of standard drinks in:
  - a mixed drink = 1 or more*
  - a pint (16 oz.) = 11
  - a fifth (25 oz.) = 17
  - 1.75 L (59 oz.) = 39

US: United States; oz.: ounces.

* It can be difficult to estimate the number of standard drinks in a single mixed drink made with hard liquor. Depending on factors such as the type of spirits and the recipe, a mixed drink can contain from 1 to 3 or more standard drinks.

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Graphic 56818 Version 5.0

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