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

INTRODUCTION — Nonalcoholic fatty liver disease (NAFLD) refers to the presence of hepatic steatosis when no other causes for secondary hepatic fat accumulation (e.g., 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.

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].

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 Hispanics (45 percent) compared with whites (33 percent) or blacks (24 percent) [11]. The higher prevalence in Hispanics was explained by a greater prevalence of obesity, though the lower prevalence in blacks 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 [5,15-17,22,24,27-33]

- 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 (odds ratio 1.23; 95% CI 1.04-1.44) [34]. 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 [35]. 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) [35]. 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 [36].

Currently, screening for NAFLD is not recommended for patients at increased risk. (See ‘Screening’ below.)

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.

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 [5,15,18,19,37]. 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 in 9 percent (19 percent of those older than 20 years of age) [37]. 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 [38].
  • 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 angiomas, 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 [39-41]. 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) [14,42-44]. 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 [22,32,39].

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.

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 [45]. Patients with NAFLD may also have positive serum autoantibodies (anti-nuclear antigen, antismooth muscle antibody), though the significance of these findings is unclear [36]. (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.

**DIAGNOSIS** — The diagnosis of nonalcoholic fatty liver disease (NAFLD) requires all of the following [36]:

- Demonstration of hepatic steatosis by imaging or biopsy
- Exclusion of significant alcohol consumption
- Exclusion of other causes of hepatic steatosis

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.

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.

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 antiliver/kidney microsomal antibody-1

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.

**Radiographic examinations** — Various radiologic methods can detect NAFLD, but no imaging modality is able to differentiate between the histologic subtypes of nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH) [46]. 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)

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 [47]. 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 [48]. However, the sensitivity appears to be decreased in patients who are morbidly obese [49,50]. In a study of 187 morbidly obese patients undergoing bariatric surgery, hepatic steatosis was present histologically in 95 percent but was only detected by ultrasound in 49 percent [49].

CT, MRI, and magnetic resonance spectroscopy — Both CT and MRI can identify steatosis but are not sufficiently sensitive to detect inflammation or fibrosis [51]. Magnetic resonance spectroscopy (MRS) has the advantage of being quantitative rather than qualitative or semiquantitative, but it is not widely available [52].

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 [53]. 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.

Unlike CT and MRI, MRS allows for quantification of hepatic fat, and may be particularly helpful in patients with small amounts of hepatic steatosis [54]. 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) [55]. 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 [56]. The only way to definitively confirm or exclude the diagnosis of NASH and to determine disease severity is with a liver biopsy [6,57]. 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.

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.
Which patients to biopsy — There is no clear consensus about which patients require a liver biopsy [58]. 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.

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 — Histologic findings in NAFLD include steatosis, inflammation, cell injury, and fibrosis. The minimum criterion for a histologic diagnosis of NAFLD is >5 percent steatotic hepatocytes in a liver tissue section [58,59]. The extent of steatosis can be described as mild (5 to 33 percent of hepatocytes are steatotic), moderate (34 to 66 percent of hepatocytes), or severe (>66 percent of hepatocytes) [60].

Patients with NAFLD typically have macrovesicular steatosis, though mixed steatosis may also be seen [60]. Pure microvesicular steatosis is uncommon. In adults, steatosis is typically first seen in acinar zone 3, though when severe it may occupy the entire acinus.

Patients with NAFL may have foci of lobular inflammation, mild portal inflammation, and lipogranulomas, but features of steatohepatitis (i.e., hepatocellular injury and fibrosis) are absent by definition.

Patients with NASH have liver biopsy findings that may be indistinguishable from those of alcoholic steatohepatitis. A diagnosis of NASH requires the findings of steatosis, hepatocyte injury (typically ballooning degeneration), and lobular inflammation (typically in acinar zone 3). Fibrosis is not a required diagnostic feature, but may be seen.

Histologic findings of NASH include (picture 1A-C) [60-62]:


Nonalcoholic steatohepatitis on biopsy

- Steatosis
- Hepatocyte swelling or ballooning degeneration
- Apoptotic (acidophil) bodies
- Mild lobular inflammation (acute, and less often, chronic)
- 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 [60]. It is possible that portal fibrosis alone may represent a variant of NASH [63]. In biopsy specimens from children, portal inflammation may be more prominent than in adults [61].

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 [60]. 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) [64]. 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 [65]. The NAS is the sum of the biopsy's individual scores for steatosis (0 to 3), lobular inflammation (0 to 2), hepatocellular ballooning (0 to 2), and fibrosis (0 to 4). An NAS of 1 or 2 corresponds to NAFL, 3 to 4 corresponds to borderline NASH, and a score ≥5 corresponds to NASH.

**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.

**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 [36]:

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*Images: Nonalcoholic steatohepatitis liver biopsy and Mallory-Denk bodies in alcoholic hepatitis.*

*Courtesy of Marshall M. Kaplan, MD.*

*Graphic 75188 Version 3.0*
Significant alcohol consumption — Several definitions have been proposed for what constitutes significant alcohol consumption \[66\]. We define significant alcohol consumption as an average consumption of >210 grams of alcohol per week in men or >140 grams of alcohol per week in women over at least a two-year period, a definition that is consistent with a 2012 joint guideline from the American Gastroenterological Association, the American Association for the Study of Liver Diseases, and the American College of Gastroenterology \[36\].

A standard drink in the United States (12 oz [360 mL] of beer, 5 oz [150 mL] of wine, 1.5 oz [45 mL] of 80-proof spirits) contains approximately 14 grams of alcohol (figure 1), so the limits above roughly translate to >15 drinks per week for men and >10 drinks per week for women.

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 \[67\]. The model is based upon aminotransferase levels, mean corpuscular volume (MCV), body mass index (BMI), and sex:

\[
ANI = -58.5 + 0.637 \text{(MCV)} + 3.91 \left(\frac{\text{AST}}{\text{ALT}}\right) - 0.406 \text{(BMI)} + 6.35
\]

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:

\[
\text{Probability} = \frac{e^{ANI}}{1+e^{ANI}}
\]

The ability of the model to accurately categorize patients ranged from good to excellent in validation cohorts \[67\].

SCREENING — One issue that arises is whether to screen patients for nonalcoholic fatty liver disease if they are at increased risk because of an associated condition such as diabetes or obesity. Currently, the American Association for the Study of Liver Diseases guidelines do not recommend screening because there are uncertainties around which diagnostic test to use (since liver enzyme
levels may be normal in patients with NAFLD), how to treat NAFLD if discovered, and whether screening is cost-effective [36]. (See 'Association with other disorders' above.)

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.)

SUMMARY AND RECOMMENDATIONS

●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.

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.

●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.

●Patients with NAFLD may have mild or moderate elevations in the aspartate aminotransferase and alanine aminotransferase, although normal aminotransferase levels do not exclude NAFLD.

●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.

●A definitive diagnosis of NAFLD requires all of the following:
  •Demonstration of hepatic steatosis by imaging or biopsy
  •Exclusion of significant alcohol consumption
  •Exclusion of other causes of hepatic steatosis

●Other causes of hepatic steatosis include:
  •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

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.

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