Fatty liver disease (steatosis), defined as storage of excessive fat in the liver, is not uncommon and there is an increasing incidence of this disease. The liver is an essential organ with multiple life-supporting functions. The liver produces bile, which helps with digestion, makes protein for the body, stores iron, converts nutrients into energy, creates substances that help your blood clot, and helps resist infections by making immune factors and removing bacteria and toxins. A healthy liver contains a small amount of fat, but too much fat buildup (steatosis) may progress to inflammation and fibrosis.

Although fatty liver disease may not prevent the liver from functioning normally, it is associated with other components of metabolic dysregulation; for 7% to 30% of people with fatty liver disease, this condition gets worse over time.

There are two main forms of fatty liver disease:
1. Alcoholic liver disease, the accumulation of fat in the liver as a result of excess intake of alcohol. About 5% of the people in the United States have this form of liver disease.
2. Nonalcoholic fatty liver disease (NAFLD), which occurs in people who do not drink in excess.

NAFLD is a type of fatty liver disease that is not related to excess alcohol consumption. There are five stages of NAFLD.
1. Simple fatty liver, in which there is fat in the liver but little or no inflammation or liver cell damage. Simple fatty liver disease typically does not cause liver damage or complications but can progress to nonalcoholic steatohepatitis (NASH) over time.
2. NASH is characterized by inflammation and liver cell damage as well as fat in the liver. Inflammation and liver cell damage may lead to fibrosis of the liver. NASH may lead to cirrhosis or liver cancer.
3. Fibrosis is characterized by persistent scar tissue in the liver and in the blood vessels around the liver.
4. Cirrhosis is when the liver stops working properly and symptoms such as jaundice and a dull ache in the lower right side of the ribs start to appear.
5. Hepatocellular carcinoma or malignancy of the liver.

It is not known why some people accumulate fat in the liver while others do not. Similarly, there is limited understanding of why some fatty livers develop inflammation that progresses to cirrhosis of the liver.

The causes and consequences of NAFLD as well as treatment options for this disease are still being investigated. This article will focus on what is currently known about nonalcoholic fatty liver (NAFL) and NASH.

Definitions
NAFLD encompasses the entire spectrum of fatty liver disease ranging from fatty liver to cirrhosis in individuals without significant alcohol consumption. Nonalcoholic fatty liver (NAFL) is defined as the presence of >5% hepatic steatosis without incidence of hepatocellular injury in the form of ballooning of the hepatocytes or evidence of fibrosis. NASH is defined as the presence of >5% hepatic steatosis and inflammation with hepatocyte injury with or without any fibrosis. The most important histological feature associated with mortality in NASH is the presence of significant fibrosis.1-3

Incidence and Prevalence of NAFLD
There are few data regarding the incidence of NAFLD in the general population. A number of publications have described the prevalence of NAFLD, and estimates of the overall global prevalence of NAFLD is about 25%.4 One estimate of the prevalence of NASH in the general population ranges between 1.5% and 6.5%.4 The prevalence of NAFLD in high-risk groups including...
individually with obesity, type 2 diabetes, dyslipidemia, metabolic syndrome, and polycystic ovary syndrome, is increased.\(^5\) The prevalence of NAFLD and the stage of liver disease appear to increase with age.\(^6\) The prevalence of NAFLD in men is two times higher than in women.\(^7\) NAFLD is the most rapidly increasing cause of liver-related mortality and is emerging as an important cause of end-stage liver disease, primary liver cancer, and liver transplantation and is associated with a substantial health economic burden.\(^6\) NASH has been recognized as one of the leading causes of cirrhosis in adults in the United States.\(^5\) NASH-related cirrhosis is the second leading indication for liver transplants.\(^8\)

The primary contributor to NAFLD is overnutrition, which causes the expansion of adipose depots as well as an accumulation of ectopic fat in areas outside of the liver, including the visceral compartment, muscle tissues, and heart. Macrophage infiltration of the visceral adipose compartment creates a proinflammatory condition that promotes insulin resistance. Inappropriate lipolysis in the setting of insulin resistance results in unabated delivery of fatty acids to the liver, which along with lipogenesis overwhelms its metabolic capacity. This imbalance contributes to cellular stress, inflammation, apoptotic cell death, tissue regeneration, and fibrogenesis.

Although liver biopsy is the gold standard used to characterize and quantify histological features of steatosis, inflammation, hepatocyte ballooning, and fibrosis, NAFLD is often identified by imaging. Abdominal ultrasonography is the most common readily available imaging modality for identifying NAFLD. When visualized on abdominal ultrasonography, hepatic steatosis is characterized by a bright liver echotexture and blurring of the hepatic vasculature. Abdominal ultrasonography has limitations: advanced fibrosis can coarsen hepatic echotexture and blur vascular patterns, and its sensitivity is low when steatosis is mild. Liver disease can be determined with noninvasive tests such as measuring liver enzymes. However, liver enzyme concentrations can be normal in more than half of the patients with NAFLD and correlate poorly with histological severity.\(^9\) The Fibrosis-4 (FIB-4) index and aspartate aminotransferase-to-platelet ratio index are diagnostic clinical and routine laboratory parameters that are inexpensive tools to estimate the severity of liver fibrosis.\(^10\) Another method to estimate liver fibrosis in patients with NAFLD is to measure liver stiffness by ultrasound elastography (Fibroscan) and magnetic resonance elastography.\(^11\)

NAFLD is a continuum of disease ranging from hepatic steatosis to NASH with or without fibrosis and cirrhosis. Studies have reported that 43%–44% of patients with steatosis progressed to NASH and that 7%–30% of NASH patients progressed to cirrhosis.

**“Lean” NAFLD**

Although NAFLD is generally associated with obesity and its comorbidities, not all patients with NAFLD are overweight or obese.\(^12\) The term metabolic dysfunction-associated fatty liver disease has been suggested to more accurately reflect the pathogenesis of the condition. No consensus has been reached on the use of this term. There is a clear relationship between metabolic syndrome and fatty liver disease. According to the Adult Treatment Panel III Guidelines, the clinical definition of metabolic syndrome requires the presence of three or more of the following features:\(^13\)

1. Waist circumference: >102 cm for men, >88 cm for women
2. Triglycerides >150 mg/dL
3. High-density lipoprotein (HDL) cholesterol: <40 mg/dL men; <50 mg/dL for women
4. Blood pressure >130/85 mm/Hg
5. Fasting glucose >110 mg/dL

Roughly 20% of patients with hepatic steatosis present with normal body mass index and 40% are not obese.\(^14\) Different mechanisms influence hepatic steatosis in lean individuals. These mechanisms include a diet high in carbohydrates/cholesterol, visceral adipose tissue (belly fat), sarcopenia, gut dysbiosis, physical inactivity, and steatogenic genetic variants.\(^15\)

**Risk Factors**

NAFLD often causes no signs or symptoms but may present as fatigue and pain or discomfort in the upper abdomen. Possible signs or symptoms of NASH and
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Cirrhosis may include abdominal swelling (ascites), enlarged blood vessels just beneath the skin’s surface, enlarged spleen, red palms, and jaundice. There are many risk factors for NAFLD. Common conditions associated with NAFLD are listed above (Table 1).

Age and sex also play a role in risk of NAFLD. The prevalence and stage of liver disease appears to increase with age. The prevalence of NAFLD in men is two times higher than in women. Obesity, type 2 diabetes, dyslipidemia, metabolic syndrome, and polycystic ovary syndrome are considered risk factors for NAFLD. Visceral adipose tissue (belly fat), identified as an increased waist circumference or waist-to-hip ratio, is a recognized contributor to significant fibrosis and NASH in patients with NAFLD. Visceral adipose tissue was originally considered a passive depot for energy storage but is now recognized as active endocrine tissue that releases many peptides and hormones that regulate metabolism, inflammation, and immunity and thus participate in the pathogenesis of NAFLD.

NASH is the second leading cause of liver transplantation. NAFLD is closely linked with cardiovascular disease (CVD) and confers significant morbidity and mortality. More patients with NAFLD die from CVD than from liver-related complications. NAFLD is identified as an independent risk factor for CVD. It is not well understood which patients with NAFLD are at highest risk for CVD. In recent studies, patients with NAFLD who experienced an incident cardiovascular event were most likely to be older, have hypertension, diabetes, lower albumin, higher total cholesterol, lower non-HDL cholesterol (non-HDL-C), and higher low-density lipoprotein cholesterol as well as lower alanine aminotransferase and aspartate aminotransferase levels.

Screening for NAFLD

NAFLD usually causes no signs or symptoms, but when it does it may include fatigue and/or pain/discomfort in the upper right abdomen. Possible signs and symptoms of NASH and advanced fibrosis or cirrhosis may include ascites, enlarged blood vessels just beneath the skin surface, enlarged spleen, red palms, and jaundice.

Because the prevalence of NAFLD is over 25% and it is a progressive disease, screening for NAFLD is essential. Although there is no consensus on who should be screened, it is generally recognized that individuals over the age of 50 who have diabetes or metabolic syndrome is significantly associated with NAFLD in HIV-infected patients.

Outcomes of NAFLD

NAFLD and its severity are associated with an increased risk of mortality. NAFLD patients with fibrosis have a higher risk of all-cause mortality than those without fibrosis, and the risk increases with increases in fibrosis stage. The most common cause of death in patients with NAFLD is cardiovascular disease independent of other metabolic comorbidities. Liver-related mortality is the 12th leading cause of death in the general population, and it is the second or third cause of death among patients with NAFLD.

Cancer-related mortality is among the top three causes of death in patients with NAFLD. Patients with histologically confirmed NASH have an increased liver-related mortality rate. The most important histological feature of NAFLD associated with long-term mortality is fibrosis. NASH is the third most common cause of hepatocellular carcinoma in the United States. Cancer-related mortality is among the top three causes of death in patients with NAFLD. NASH is the second leading cause of liver transplantation.

Metabolic syndrome is significantly associated with NAFLD in HIV-infected patients.

Table 1

<table>
<thead>
<tr>
<th>RISK FACTORS ASSOCIATED WITH NAFLD</th>
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<tr>
<td><strong>Common conditions associated with NAFLD</strong></td>
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<td>Obesity</td>
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<td>Type 2 diabetes</td>
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<td>Dyslipidemia</td>
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<td>Metabolic syndrome</td>
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<td>Polycystic ovary syndrome</td>
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<td><strong>Other conditions associated with NAFLD</strong></td>
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<tr>
<td>Hypothyroidism</td>
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<td>Obstructive sleep apnea</td>
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<td>Hypopituitarism</td>
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<td>Hypogonadism</td>
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<td>Pancreaticoduodenal resection</td>
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<td>Psoriasis</td>
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Nonalcoholic liver disease often causes no signs or symptoms but may present as fatigue and pain or discomfort in the upper abdomen. Possible signs or symptoms of nonalcoholic steatohepatitis and cirrhosis may include abdominal swelling (ascites), enlarged blood vessels just beneath the skin’s surface, enlarged spleen, red palms, and jaundice.

syndrome should be screened. Screening could be further expanded to include patients with CVD or HIV infection since they are at increased risk for NAFLD. Signs of NAFLD often present as incidental findings during routine care, such as elevated liver enzymes or fatty infiltration in the liver seen on imaging for another ailment.

NAFLD is often a diagnosis of exclusion. It is reasonable to rule out other causes of elevated liver enzymes, such as viral hepatitis or certain autoimmune disorders, before suspecting NAFLD.

Typical tests done in screening for NAFLD includes:

1. Blood tests
   a. Complete blood count
   b. Liver enzymes and liver function tests
   c. Tests for chronic viral hepatitis
   d. Celiac disease screening
   e. Fasting blood sugar
   f. Hemoglobin A1C
   g. Lipid profile

2. Imaging Studies
   a. Abdominal ultrasound
   b. Computerized tomography
   c. Vibration controlled transient elastography— to measure stiffness of the liver

3. Liver Biopsy
   a. Liver biopsy is the current gold standard for diagnosing NAFLD

Three tools useful in screening are the NAFLD fibrosis score (NFS), the Fibrosis 4 Score (FIB-4), and the enhanced liver fibrosis (ELF) score. The NFS is a clinical prediction rule to identify patients with more advanced fibrosis. The NFS uses blood laboratory tests (platelet count, albumin, and aspartate aminotransferase) and body parameters (age, body mass index, and impaired fasting glucose/diabetes) to reliably diagnose advanced fibrosis. The FIB-4 that is also used to predict advanced fibrosis uses laboratory values (aspartate aminotransferase, alanine aminotransferase, and platelets) and a clinical parameter (age). The ELF score is a noninvasive blood test that measures three direct markers of fibrosis: hyaluronic acid, procollagen III amino-terminal peptide, and tissue inhibitor of matrix metalloproteinase. These tools are easy to use and reliable in determining the presence of advanced fibrosis.

Management of Patients with NAFLD

The management of patients with NAFLD currently consists of lifestyle modifications as well as treatment of associated comorbidities such as obesity, hyperlipidemia, insulin resistance, and diabetes. Currently there are no U.S. Food and Drug Administration (FDA)-approved treatments for NAFLD.

Recommendations for lifestyle modifications may consist of weight loss, exercise, and dietary changes, with weight loss being the key to reducing fibrosis. A calorie-restricted diet over time is associated with mobilization of liver fat and reduction in cardiovascular risk. Data suggest that decreasing caloric intake by at least 30% or by approximately 750–1000 kcal/day results in improvement of insulin resistance and hepatic steatosis. Weight loss of at least 3%–5% of body weight appears necessary to improve steatosis but a greater weight loss of 7%–10% is needed to reduce fibrosis. Weight loss can be difficult to achieve and sustain in most patients. Bariatric surgery decreases or eliminates comorbid disease and improves long-term survival and death from CVD and malignancy, the two most common causes of death in patients with NAFLD. Most patients with NAFLD engage in minimal physical activity, which further contributes to development of metabolic syndrome and NAFLD. Data suggest that patients who maintain physical activity of more than 150 minutes/week or increase their activity level by more than 60 minutes/week have a significant reduction in serum aminotransferases, independent of weight loss.

Drug Development for NAFLD/NASH

Currently there are no FDA-approved drugs for the treatment of NAFLD/NASH. As previously stated, first-line treatment for NAFLD is lifestyle modification, including diet and exercise, followed by off-label
generic drugs such as vitamin E, pioglitazone, and pentoxifylline. However, data on the use of these options is limited, and thus they should only be considered for patients with biopsy-proven NASH. There are many challenges to drug development for the treatment of NAFLD/NASH. These challenges include the gradual and slow progress of chronic inflammatory changes in the liver, potential lifelong treatment, vulnerability to comorbidities, and limitations in monitoring. Clinical trials have investigated anti-inflammatory, antifibrotic, and metabolic drugs for the treatment of NAFLD/NASH. Many investigational agents have failed to achieve the desired clinical outcomes and were stopped at the conclusion of phase 2. However, many trials are still ongoing.

Case Management
What is the role of the case manager for patients with NAFLD? Diagnosis of NASH is important because it generally presents without signs or symptoms. The case manager assesses patients, supports a treatment plan, monitors patients, and educates patients about NAFLD. It is essential for case managers who work with patients with NAFLD/NASH to be proactive.

Case managers need to first identify patients who are at risk for NAFLD and NASH. Patients at risk include those with obesity, type 2 diabetes, dyslipidemia, metabolic syndrome, HIV infection, obstructive sleep apnea, hypogonadism, hypothyroidism, hypopituitarism, increased visceral fat (hard belly fat), or elevated liver enzymes in the absence of other etiologies. The case manager should ensure that all comorbidities are recognized and well managed while working with the patient and the patient’s healthcare team. Monitoring associated comorbidities (eg, glucose monitoring, weight, waist circumference, waist-to-hip ratio, and blood values) is essential. If weight loss and exercise are indicated, a realistic and specific program should be developed in conjunction with the patient and healthcare team. A weight loss diet and exercise program are challenging for most people. Designing one that is realistic, sustainable, and with built-in monitoring is important.

Education is a key factor in a successful outcome for patients at risk for or who have a confirmed diagnosis of NAFLD and NASH. The greater the understanding the patient has of the disease, signs and symptoms, and treatment, the better the outcome. Patient education takes many forms and needs to be tailored for individual patients. Education takes time, particularly since NAFLD and NASH are chronic diseases. Continued evaluation and support are essential. Monitoring may lead to changes in the plan in order to meet the patient’s goals.

Since there are no approved drugs for NAFLD/NASH, case managers can educate patients about appropriate clinical trials for NAFLD/NASH. NAFLD affects a significant percentage of the population and has long-term consequences. The key to successful management of NAFLD is being proactive. Given that the disease doesn’t present with signs and symptoms, identification of patients at risk for NAFLD is essential. Using the case management process, the case manager can help the patient achieve the desired outcomes.

References


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**Nonalcoholic Fatty Liver Disease: A Case Management Primer**

**Questions**

1. Which of the following are functions of the liver?
   a. Produce bile, which helps digestion
   b. Make protein for the body
   c. Store iron
   d. All of the above

2. A healthy liver contains a small amount of fat but becomes problematic when steatosis progresses to a state of inflammation and fibrosis.
   a. True  
   b. False

3. How many stages of nonalcoholic fatty liver disease (NAFLD) are there?
   a. 2
   b. 4
   c. 5
   d. 7

4. The difference between NAFLD and nonalcoholic steatohepatitis (NASH) is the presence of hepatocyte injury.
   a. True  
   b. False

5. What is the global prevalence of NAFLD?
   a. 17%
   b. 19%
   c. 22%
   d. 25%

6. Which of the following risk groups have a higher prevalence of NAFLD?
   a. Obese patients
   b. Patients with type 2 diabetes
   c. Patients with metabolic syndrome
   d. All of the above

7. NAFLD is often diagnosed with abdominal ultrasonography.
   a. True  
   b. False

8. All patients with NAFLD are obese.
   a. True  
   b. False

9. Possible signs and symptoms of NASH and cirrhosis may include:
   a. Ascites
   b. Enlarged spleen
   c. Jaundice
   d. All of the above

10. The most common cause of death in patients with NAFLD is cardiovascular disease.
    a. True  
    b. False

11. The U.S. Food and Drug Administration has not approved a drug for the treatment of NAFLD/NASH, but there are several clinical trials in progress.
    a. True  
    b. False

12. The case management plan for patients with NAFLD includes:
    a. Identifying patients at risk for NAFLD
    b. Managing the comorbidities associated with NAFLD
    c. Education
    d. All of the above

(CE Exam continues)
Nonalcoholic Fatty Liver Disease: A Case Management Primer

Objectives

a. Define fatty liver disease.
b. State four common conditions that are associated with nonalcoholic fatty liver disease.
c. Define the role of the case manager for patients with nonalcoholic fatty liver disease.

Please indicate your answer by filling in the letter:


Continuing Education Program Evaluation

Please indicate your rating by circling the appropriate number using a scale of 1 (low) to 5 (high).

1. The objectives were met. 1 2 3 4 5
2. The article was clear and well organized. 1 2 3 4 5
3. The topic was both relevant and interesting to me. 1 2 3 4 5
4. The amount and depth of the material were adequate. 1 2 3 4 5
5. The quality and amount of the graphics were effective. 1 2 3 4 5
6. I would recommend this article. 1 2 3 4 5
7. This has been an effective way to present continuing education. 1 2 3 4 5
8. How will this activity impact your practice? ______________________________________
9. Additional comments: __________________________________________________________

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