NAFLD & NASH

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- **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.

NAFLD ---→ NASH ---→ FIBROSIS --→ CIRRHOSIS

- 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

- 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.

- Patients with NAFLD (particularly those with NASH) often have one or more components of the metabolic syndrome:
- Obesity
- Systemic hypertension
- Dyslipidemia
- Insulin resistance or overt diabetes

- 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.**

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.

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.
- 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.
- Patients who have developed cirrhosis may have stigmata of chronic liver disease (eg, palmar erythema, spider angiomata, ascites)….

Laboratory findings

- Patients with NAFLD may have mild or moderate elevations in the aspartate aminotransferase (AST) and alanine aminotransferase (ALT) , although normal aminotransferase levels do not exclude NAFLD .
- 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.
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- 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) .
- **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**.

- 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 and cytopenias.

- Patients with NAFLD may have an elevated serum ferritin concentration or transferrin saturation .
- 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.
- Patients with NAFLD may also have positive serum autoantibodies (antinuclear antigen, antismooth muscle antibody), though the significance of these findings is unclear.

Radiographic findings

- Radiographic findings in patients with NAFLD include increased echogenicity on ultrasound
- decreased hepatic attenuation on computed tomography (CT)
- and an increased fat signal on magnetic resonance imaging (MRI).

DIAGNOSIS

- The diagnosis of nonalcoholic fatty liver disease (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

- 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).

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.
- 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 obtain the following tests in all patients:

- Anti-hepatitis C virus antibody
- Hepatitis A IgG
- Hepatitis B surface antigen, Hbs Ab, and Hbc Ab
- Plasma iron, ferritin, and total iron binding capacity
- Serum gammaglobulin level, antinuclear antibody, antismooth muscle antibody, and anti-liver/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) .
- 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
- 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.

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.**
- **The only way to definitively confirm or exclude the diagnosis of NASH and to determine disease severity is with a liver biopsy.**

- 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.

Which patients to biopsy

- **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.
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- 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) .

- Patients with NAFLD typically have macrovesicular steatosis.
- A diagnosis of NASH requires the findings of steatosis, hepatocyte injury (typically ballooning degeneration), and lobular inflammation (typically in acinar zone 3).

DIFFERENTIAL DIAGNOSIS

- **Causes of hepatic steatosis in addition to NAFLD include :**
- 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)

Risk factors for progression

- One of the most important risk factors is histologic evidence of hepatic inflammation.

- Other factors that have been associated with disease progression or advanced fibrosis include:
  - Age greater than 45 or 50 years
  - Diabetes mellitus
  - Elevated serum aminotransferases (≥2 times the upper limit of normal in one study)
  - Presence of ballooning degeneration plus Mallory hyaline or fibrosis on biopsy
  - Body mass index ≥28 kg/m ^{2}
  - Higher visceral adiposity index, which takes into account waist circumference, body mass index, triglycerides, and high-density lipoprotein level
  - Coffee consumption has been associated with a lower risk of progression

- **Heavy alcohol use** among patients with or at risk for NAFLD is associated with hepatic steatosis, hepatic injury, and fibrosis progression.

Hepatocellular carcinoma

- Hepatocellular carcinoma (HCC) is associated with cirrhosis due to NAFLD.
- HCC surveillance is recommended for patients with NASH-related cirrhosis.

Recurrence following liver transplantation

- Recurrence of NAFLD has been reported following liver transplantation.

Mortality

- Cardiovascular disease is the most common cause of death among patients with NAFLD, though patients with NASH are at increased risk for liver-related death compared with patients without NASH .
- The association with cardiovascular disease suggests that there should be a reduced threshold for surveillance for cardiovascular disease in patients with NAFLD or NASH.

MANAGEMENT

- **General approach to the patient**
- **Weight loss** is the only therapy with reasonable evidence suggesting it is beneficial and safe.

We recommend the following approach in patients with nonalcoholic fatty liver (NAFL) or NASH:

- Weight loss for patients who are overweight or obese: Options to promote weight loss include lifestyle modifications and, for patients who are candidates, bariatric surgery.
- A reasonable goal for many patients is to lose 0.5 to 1 kg/week (1 to 2 lb/week).
- Pharmacologic therapy can be used to aid with weight loss in patients who fail to achieve weight loss goals through diet and exercise alone.

- Hepatitis A and B vaccinations should be given to patients without serologic evidence of immunity.
- Additional vaccines recommended for patients with chronic liver disease include pneumococcal vaccination and standard immunizations recommended for the population in general (eg, influenza, diphtheria, tetanus boosters) .

Treatment of risk factors for cardiovascular disease:

- Patients with NAFLD are at increased risk for cardiovascular disease and often have multiple cardiovascular disease risk factors. Management of patients with NAFLD includes optimization of blood glucose control in patients with diabetes and treatment of hyperlipidemia.
- Statin therapy has been shown to be safe in patients with NAFLD.

- In general, we do not suggest using pharmacologic agents (eg, vitamin E, pioglitazone) solely for the treatment of NAFLD.
- However, we do suggest vitamin E at a dose of 400 int. unit/day for the subset of patients with **advanced fibrosis** on biopsy who **do not have diabetes or coronary artery disease**.

- We suggest that patients with NAFLD avoid all alcohol consumption.
- **Heavy alcohol use** is associated with disease **progression** among patients with NAFLD.

Weight loss

- Weight loss and increased physical activity can lead to sustained improvement in liver enzymes, histology, serum insulin levels, and quality of life in patients with NAFLD, and we recommend weight loss for all patients with NAFLD who are overweight or obese.

- A reasonable goal for many patients is to lose 0.5 to 1 kg/week (1 to 2 lb/week).
- **More rapid weight reduction may be associated with worsening of liver disease.**

bariatric surgery

- Histologic improvement has also been observed after bariatric surgery

Pharmacologic therapies

- we do not suggest using pharmacologic agents (eg, vitamin E, pioglitazone) solely for the treatment of NASH.

Vitamin E

- Vitamin E decreases oxidative stress.
- increase in all-cause mortality with high-dose vitamin E supplementation (>400 int. unit/day).
- We suggest vitamin E at a dose of 400 int. unit/day for patients with advanced fibrosis on biopsy who do not have diabetes or coronary artery disease.

Insulin-sensitizing agents

- Whereas the thiazolidinediones have been shown to improve histologic parameters in patients with NASH, metformin has not.
- However, thiazolidinediones are associated with significant side effects and are thus not routinely used for the treatment of NASH.

Thiazolidinediones

- Thiazolidinediones, including pioglitazone and rosiglitazone , are insulin-sensitizing agents that improve liver biochemical and histologic parameters in patients with NASH .
- However, their use is associated with adverse events, including weight gain, painful swollen legs, and heart failure.
- Our approach is to use thiazolidinediones for the treatment of NASH only in patients with type 2 diabetes who are otherwise candidates for treatment with a thiazolidinedione.

Metformin

- it does not appear to be effective for the treatment of NASH.

Orlistat

- Orlistat is a gastrointestinal lipase inhibitor used in the treatment of obesity and type 2 diabetes mellitus.
- We suggest using orlistat when needed as an adjunct for weight loss, but not as a primary treatment for NASH.

Ursodeoxycholic acid

- larger randomized trials have failed to show a benefit.

Probucol

- Probucol is a lipid lowering agent with antioxidant properties.
- more patients in the probucol group achieved normal aminotransferase levels than controls (50 versus 0 percent). However, the effect on liver histology was not assessed. Probucol is not available in the United States.

Losartan

- **Angiotensin II** is involved in the **pathogenesis of hepatic fibrosis** and enhances iron deposition and insulin resistance.
- A pilot study of the angiotensin II receptor antagonist losartan in seven patients with NASH suggested a benefit on blood markers of hepatic fibrosis and serum aminotransferase levels . Further studies are needed.

Atorvastatin

- Pilot studies found a benefit from atorvastatin on aminotransferase levels in patients with NAFLD.

Pentoxifylline

- Pentoxifylline inhibits production of tumor necrosis factor-alpha, which has been hypothesized to contribute to the progression of NASH.
- Biochemical improvement, and in some cases histologic improvement, was described in several pilot studies

Omega-3 fatty acids

- treatment with omega-3 fatty acids was associated with improvement in hepatic steatosis as well as aspartate aminotransferase levels.

Patients with cirrhosis

- The management of cirrhosis due to NAFLD is similar to that for cirrhosis due to other causes and includes :
- management of portal hypertension
- screening for hepatocellular carcinoma
- and consideration of liver transplantation for patients with decompensated cirrhosis.
- Patients with NASH-related cirrhosis should undergo screening for hepatocellular carcinoma.

Follow-up liver biopsy

- In patients **who have never had a liver biopsy**, or who had a liver biopsy that **showed steatosis but not steatohepatitis**, we obtain a liver biopsy if the physical examination or laboratory findings suggest progressive liver disease.

Findings suggestive of progressive liver disease include:

- Peripheral stigmata of chronic liver disease (suggestive of cirrhosis)
- Splenomegaly (suggestive of cirrhosis)
- Cytopenias (suggestive of cirrhosis)
- Serum ferritin >1.5 times the upper limit of normal (suggestive of NASH and advanced fibrosis)
- Age >45 years with associated obesity or diabetes (increased risk of advanced fibrosis)

- In patients who had a baseline liver biopsy that showed NASH and who have a **stable** or **improving physical examination** and **laboratory findings**, we repeat a liver biopsy in five to seven years to assess disease progression.
- We obtain a liver biopsy sooner if there is evidence of worsening liver disease.