



NAFLD: The Skinny on Fatty Liver Disease

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Learning Objectives

- ▶ Recognize the prevalence and pathophysiology of NAFLD.
- ▶ Discuss important outcomes in patients with NAFLD.
- ▶ Identify the clinical manifestations of patients with NAFLD.
- ▶ Describe the evaluation and diagnosis of NAFLD.
- ▶ Outline the management and treatment of patients with NAFLD.

Prevalence of NAFLD and NASH

- ▶ 30-50 years of age, but patients are getting younger and younger
- ▶ Estimated to be 5-10% in children
- ▶ Estimated that the overall global prevalence of NAFLD diagnosed by imaging is around 25.24%
- ▶ NASH: Men > Women, incidence increases in women after age 50
- ▶ The prevalence of NASH among NAFLD patients who had liver biopsy is estimated to be 59.10%

Prevalence in High-Risk Populations

- ▶ The majority (>95%) of patients with severe obesity undergoing bariatric surgery will have NAFLD.
- ▶ Some studies suggest that one third to two thirds of patients with T2DM have NAFLD.
- ▶ The incidence of NAFLD in patients with dyslipidemia attending lipid clinics has been estimated to be 50%.

Important Outcomes of NAFLD

- ▶ Increased overall mortality compared with matched control populations
- ▶ CV is the most common cause of death (38%) in patients with NAFLD independent of other metabolic co-morbidities
- ▶ Liver-related mortality is the 12th leading cause of death in the general population, but is the 2nd or 3rd cause of death in patients with NAFLD
- ▶ NAFLD is considered third leading cause HCC in the US (increasing 9% annually)

What is NAFLD?

A spectrum of varying degrees of fatty infiltration of the liver, from steatosis to cirrhosis

AASLD Definition: There must be evidence of hepatic steatosis, either by imaging or histology and lack of secondary causes of hepatic fat accumulation

Majority of cases are associated with metabolic comorbidities such as obesity, DM, and dyslipidemia

What is NAFL?

AASLD Definition: Defined as the presence of greater than or equal to 5% hepatic steatosis without evidence of hepatocellular injury in the form of hepatocyte ballooning.

Histologic diagnosis

The risk of progression to cirrhosis and liver failure is considered minimal

What is NASH?

Non-Alcoholic Steatohepatitis is a subset of NAFLD

AASLD Definition: Presence of greater than or equal to 5% hepatic steatosis with inflammation and hepatocyte injury (ballooning) with or without fibrosis.

Histologic diagnosis

Increased incidence of progression to cirrhosis, liver failure, and hepatocellular cancer

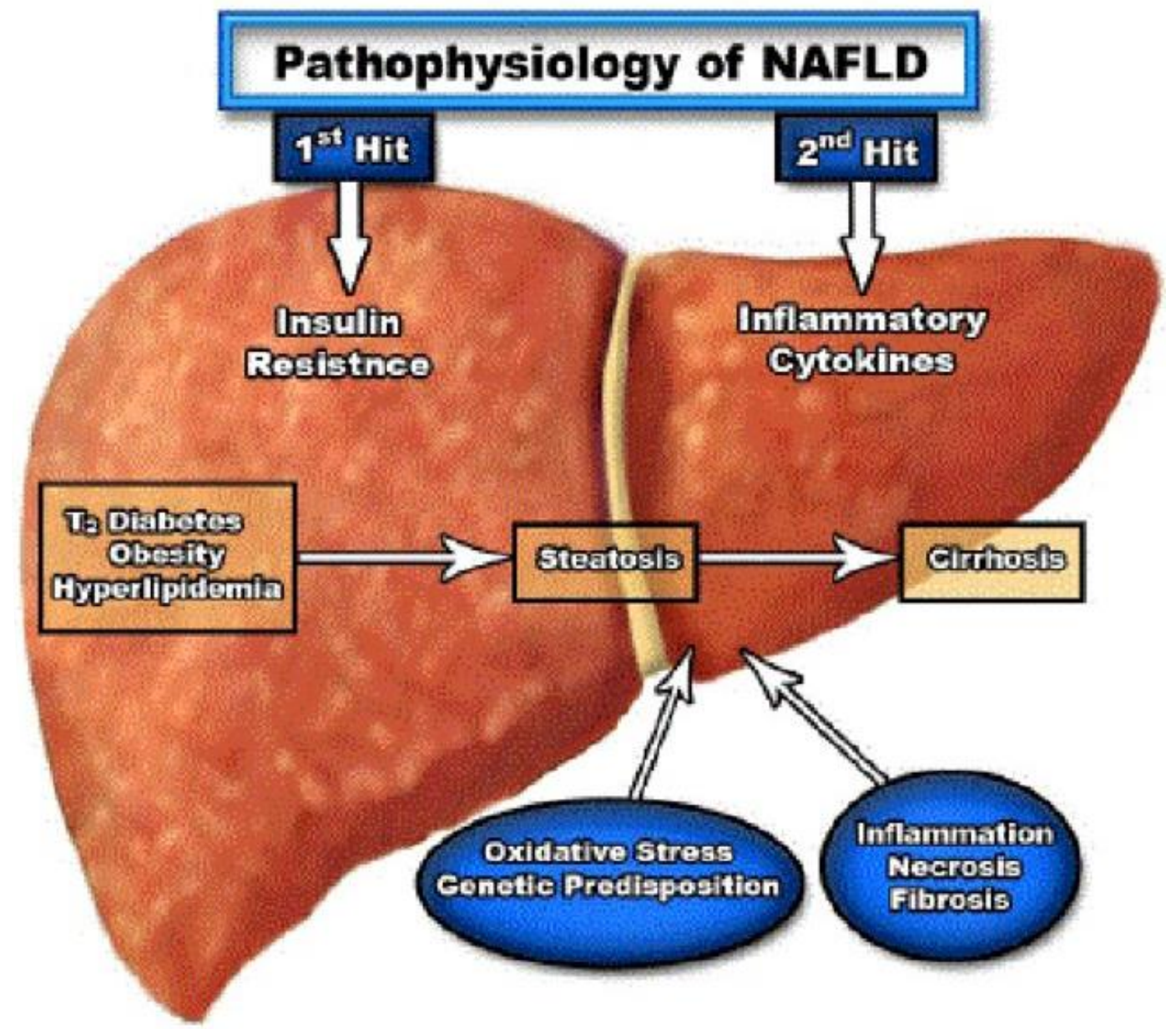
The Skinny on Definitions

NAFLD: Your patient has fat in their liver, seen either on imaging or histology, and you haven't found any secondary causes to explain the fat in the liver. Explore why!

NAFL: Your patient had a liver biopsy that showed fat in the liver without liver injury (low risk for progression at this time).

NASH: Your patient had a liver biopsy that showed fat in the liver with evidence of liver injury (increased risk for progression to advanced liver disease and complications). Be aggressive in management!

Pathophysiology



Pathophysiology: The Skinny

A normal liver has the capacity to store some fat in the form of lipids

A crucial function of a healthy hepatocyte is to metabolize macronutrients

Excess build up of fat (hepatic steatosis) can impair liver function and cellular health

When cellular health is compromised, inflammation ensues (steatohepatitis)

Followed by liver damage (fibrosis) with potential progression to end-stage liver disease (cirrhosis) and HCC (liver cancer)

Risk Factors associated with NAFLD

Obesity

T2DM

Dyslipidemia

Metabolic Syndrome

Polycystic Ovarian Syndrome

- ▶ Hypothyroidism
- ▶ Obstructive Sleep Apnea
- ▶ Hypopituitarism
- ▶ Hypogonadism
- ▶ Pancreatoduodenal Resection
- ▶ Psoriasis

Presentation

- ▶ **Patients are usually asymptomatic and NAFLD is “picked up incidentally”**
- ▶ **Occasionally, patients may complain of fatigue or RUQ abdominal discomfort**
- ▶ **Obesity, especially truncal adiposity, is the most common physical sign of NAFLD**
- ▶ **Hepatomegaly occurs in 10% of patients**

Presentation

- ▶ **Symptoms of advanced disease:**

- ▶ **Abdominal distention**
- ▶ **Pruritus**
- ▶ **Confusion**
- ▶ **Easy bruising/bleeding**
- ▶ **Edema**

- ▶ **Stigmata of advanced disease:**

- ▶ Jaundice
- ▶ Palmar erythema
- ▶ Spider angiomas
- ▶ Hepatic encephalopathy
- ▶ Asterixis
- ▶ Gynecomastia
- ▶ Hepatomegaly
- ▶ Splenomegaly





DermNetNZ.org





Evaluation of NAFLD: Biochemistries

- ▶ **Liver chemistries are often normal, but it is worth assessing a liver panel**
 - ▶ AST and ALT may be mildly elevated
 - ▶ Isolated Alk Phos occurs in about 10% of patients
- ▶ **If advanced liver disease is suspected, check synthetic function**
 - ▶ CBC, CMP, INR (AFP if concerned for advanced disease or HCC)
- ▶ **Assess for associated co-morbidities**
 - ▶ DM or insulin resistance, dyslipidemia

Remember...

To Define NAFLD:

- ▶ There must be evidence of hepatic steatosis, either by imaging or histology

and

- ▶ A lack of secondary causes of hepatic fat accumulation

Secondary Causes of Hepatic Steatosis

- ▶ **Excessive alcohol consumption**
- ▶ **Hepatitis C**
- ▶ **Autoimmune liver disease**
- ▶ **Genetic liver disease**
 - ▶ Hemochromatosis
 - ▶ Wilson's Disease
 - ▶ A1AT Syndrome
- ▶ **Medications**
 - ▶ Methotrexate, amiodarone, tamoxifen, valproate, anti-retrovirals, mipomersen, lomitapide, corticosteroids
- ▶ Parental nutrition
- ▶ Inborn errors of metabolism
- ▶ Starvation
- ▶ Lipodystrophy
- ▶ Reye Syndrome
- ▶ Abetalipoproteinemia
- ▶ Acute fatty liver of pregnancy
- ▶ HELLP Syndrome

Evaluation for Co-Existing Liver Diseases

Autoimmune liver disease:

- ▶ ANA with titer (33% NAFLD patients have an elevated ANA)
- ▶ ASMA
- ▶ AMA (associated with Primary Biliary Cholangitis)
- ▶ Immunoglobulins
- ▶ TSH

Hepatitis B and C serology

Genetic liver disease

- ▶ Iron panel, Ferritin (Hemochromatosis) (Ferritin elevated in 40-58% patients with NAFLD)
- ▶ A1AT level (Alpha-1 Antitrypsin Deficiency Syndrome)
- ▶ Ceruloplasmin (Wilson's Disease)

Alcohol Consumption

By definition, NAFLD indicates the lack of evidence for ongoing or recent consumption of significant amounts of alcohol.

So, what does significant mean?

AASLD Guidance Statement

- ▶ Ongoing or recent alcohol consumption
 - ▶ **>21 standard drinks on average per week in men**
 - ▶ **>14 standard drinks on average per week in women**
 - ▶ **Standard alcoholic drink is any drink that contains about 14 g of pure alcohol**
- ▶ Reasonable thresholds for significant alcohol consumption when evaluating patients with suspected NAFLD

NIAAA Definitions for ETOH Consumption

- ▶ NIAAA defines binge drinking as a pattern of drinking alcohol that brings blood alcohol concentration (BAC) to 0.08 percent - or 0.08 grams of alcohol per deciliter - or higher. For a typical adult, this pattern corresponds to consuming 5 or more drinks (male), or 4 or more drinks (female), in about 2 hours
- ▶ NIAAA defines heavy drinking as follows:
 - For men, consuming more than 4 drinks on any day or more than 14 drinks per week
 - For women, consuming more than 3 drinks on any day or more than 7 drinks per week

U.S. Department of Health & Human Services

- ▶ **Drinking in Moderation:**

- ▶ According to the "Dietary Guidelines for Americans 2020-2025," U.S. Department of Health and Human Services and U.S. Department of Agriculture:

- Adults of legal drinking age can choose not to drink or to drink in moderation by limiting intake to 2 drinks or less in a day for men and 1 drink or less in a day for women, when alcohol is consumed.

- Drinking less is better for health than drinking more.

Evaluation of NAFLD: Imaging

- ▶ Liver sonogram commonly identifies hepatic steatosis
 - ▶ Commonly described as diffuse echogenicity of the liver parenchyma
- ▶ If concerned about more advanced liver disease, order as an abdominal sonogram
 - ▶ This will assess for HSM and ascites, along with assessment of the liver
- ▶ If concerned about cirrhosis and/or HCC:
 - ▶ Triphasic CT with liver mass protocol or MRI liver

Non-Invasive Assessment of Fibrosis

- ▶ **NAFLD Fibrosis Score (NFS)**

- ▶ Predictive calculator of fibrosis based on age, BMI, glucose impairment, platelet count, albumin, and AST/ALT ratio (+ predictive value of 90%)

- ▶ **Fibrosis 4 Score**

- ▶ Predictive calculator of fibrosis based on age, platelet count, and AST and ALT levels

- ▶ **Vibration-Controlled Transient Elastography (FibroScan)**

- ▶ Using an US probe, measures the shear wave velocity (amount of time it takes for a sound wave to flow through the liver) to predict liver stiffness

- ▶ **Magnetic Resonance Elastography (MRE)**

- ▶ Acoustic radiation force impulse imaging and supersonic shear wave elastography

Evaluation: Liver Biopsy

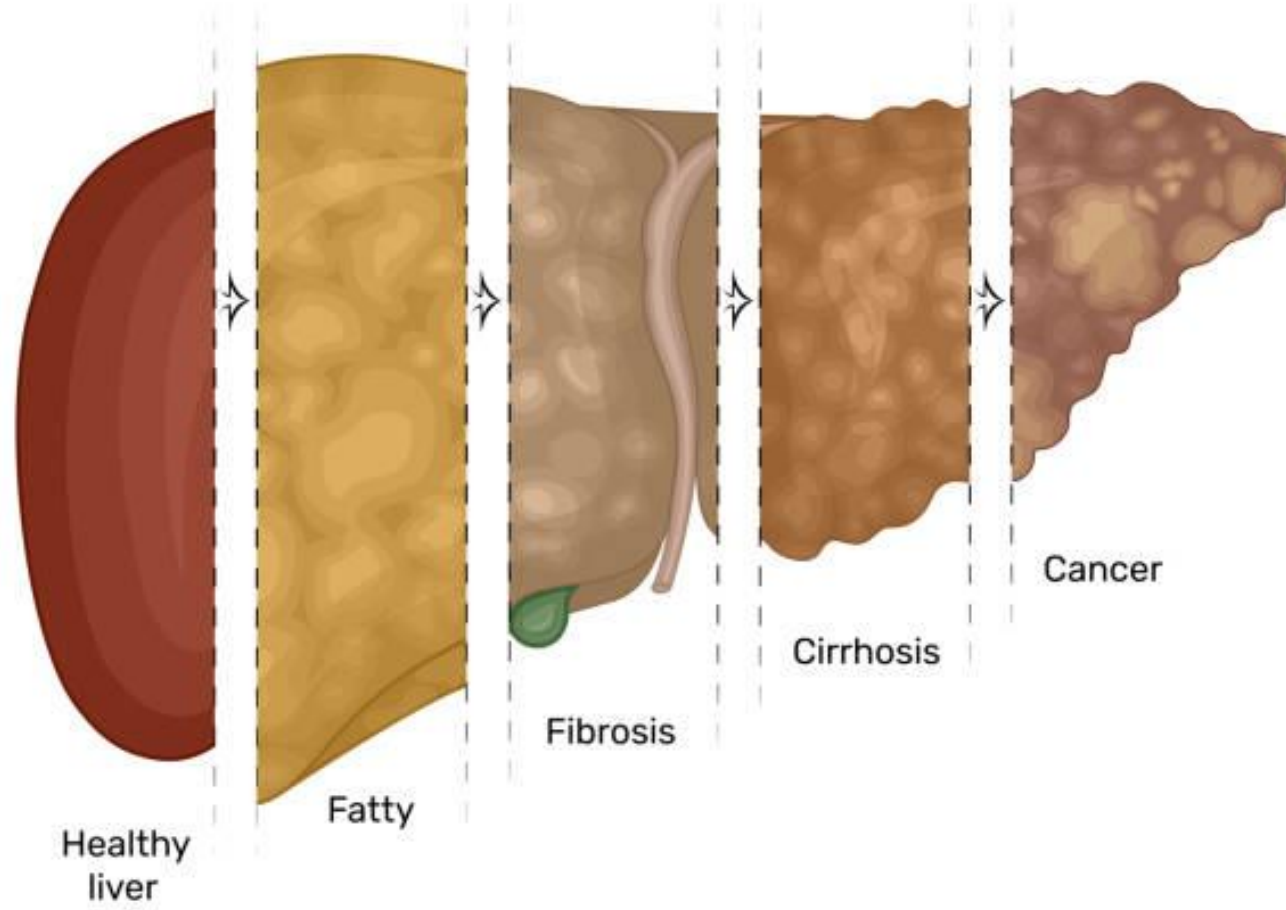
- ▶ **Most effective diagnostic tool for identifying NAFLD**
 - ▶ Confirm diagnosis
 - ▶ Rule out other causes of liver disease
 - ▶ Delineate simple steatosis (NAFLD) from steatohepatitis (NASH)
 - ▶ Assessing degree of fibrosis (Stage 0-4)

Evaluation: Liver Biopsy

▶ AASLD Guidance Statements:

- ▶ Liver bx should be considered in patients with NAFLD who are at increased risk of having NASH and/or advanced fibrosis
- ▶ The presence of metabolic syndrome, NFS or FIB-4, or liver stiffness measured by FibroScan or MRE may be used to identify patients who are at risk for NASH and/or advanced fibrosis.
- ▶ Liver bx should be considered in patients with suspected NAFLD in who competing etiologies for HS and the presence and/or severity of co-existing chronic liver disease cannot be excluded without a liver bx

Stages of liver damage



Treatment of NAFLD



Diet and lifestyle modifications



Pharmacotherapy



Supplements



Bariatric Surgery

Treatment: Diet and Lifestyle Changes



Mediterranean diet is widely recommended

-Anti-oxidant and anti-inflammatory benefits



Weight loss

-5% can reduce steatosis

-10% can improve cellular inflammation that leads to fibrosis



Exercise

-At least 200 minutes of walking/week

Treatment: Pharmacotherapy

- ▶ **No medications are currently FDA-approved to treat NAFLD or NASH**
- ▶ **Insulin Sensitizers**
 - ▶ Metformin showed positive effects on IR, but no improvement in liver histology
 - ▶ Pioglitazone improvement in liver histology, but because of concerns of adverse effects, AASLD does not recommend the use to treat NAFLD without bx-proven NASH until more data is available to show safety and efficacy
- ▶ **Weight Loss Medications**
 - ▶ FDA-approved for obesity, but not specifically approved for NAFLD
- ▶ **Statins**
 - ▶ FDA-approved for lipid management, but not for NAFLD

Treatment: Supplements

▶ **Vitamin D**

- ▶ 50% of patients with NAFLD were deficient in Vit D, although relationship is not well understood

▶ **Vitamin E**

- ▶ Daily dose of 800 IU improves liver histology in nondiabetic adults with biopsy-proven NASH and can be considered for this patient population
- ▶ AASLD guidance does not recommend Vitamin E to treat NASH in diabetic patients, NAFLD without liver biopsy, NASH cirrhosis, or cryptogenic cirrhosis

▶ **Omega-3 Fatty Acids**

- ▶ Not recommended for NAFLD due to insufficient supporting data
- ▶ Can be considered for lipid management in patients with NAFLD

Treatment: Bariatric Surgery

- ▶ **AASLD Guidance Statements:**

- ▶ Bariatric surgery can be considered in otherwise eligible obese individuals with NAFLD or NASH
- ▶ Histologic steatosis, ballooning, and fibrosis all improved in patients who underwent bariatric weight loss surgery
- ▶ It is premature to consider bariatric surgery as an established option specifically to treat NASH

Which statement is correct about NAFLD?

- ▶ A. It is an independent predictor for CVD & estimated to be associated with more than 68%.
- ▶ B It is estimated to be associated with 38% of all cancers.
- ▶ C. NASH is a benign sub-set of NAFLD
- ▶ D. It is a spectrum of varying degrees of fatty infiltration, from hepatic steatosis to cirrhosis without secondary causes for fat accumulation.

Which statement is correct about the prevalence of NAFLD?

- ▶ A. NAFLD is never found in children
- ▶ B. Prevalence peaks in patients who are age 30-50, then declines
- ▶ C. In patients under age 50 years, NASH is more common in men than women
- ▶ D. The incidence decrease in women after age 50 years, perhaps because of postmenopausal hormone changes

Which statement is correct about the initial presentation of NAFLD?

- ▶ **A. Obesity, especially truncal adiposity, is the most common and often only physical sign of NAFLD**
- ▶ Most patients are symptomatic with RUQ abd pain at initial presentation
- ▶ Hepatomegaly is present in about 40% of patients with NAFLD
- ▶ Jaundice is commonly seen in the initial presentation



Which imaging modality is the most useful in the initial evaluation of NAFLD?

A. Liver CT

B. MRI

C. Abd Sono

D. Flat Plate Radiograph of Abd

Which statement is true about the treatment of NAFLD?

- A. Several FDA-approved medications are available to treat NAFLD
- B. A modest weight loss of 5% has been shown to reduce steatosis; 10% weight loss can improve necroinflammation that leads to cirrhosis
- C. Vitamin D has demonstrated effectiveness in improving liver histology
- D. Studies have shown no histologic changes in patients with NASH that had bariatric surgery

QUESTIONS?

THANK YOU