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DIAGNOSIS of Nonalcoholic fatty liver disease (NAFLD)

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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.

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

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
- ●Absence of coexisting chronic liver disease

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.

Association with other disorders

- 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

metabolic syndrome was associated with an increased risk of severe fibrosis

- 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.

There are also data that suggest NAFLD is associated with cholecystectomy.

- 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

Currently, **screening** for NAFLD is **not recommended** for patients at increased risk.

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 .In some patients, hepatomegaly is the presenting sign of NAFLD. The reported prevalence of hepatomegaly in patients with NAFLD is highly variable:
- 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).

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. 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, thrombocytopenia, and neutropenia.

- 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

- 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 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 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 routinely used 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.

Ultrasound

- Ultrasonography often reveals a hyperechoic texture or a bright liver because of diffuse fatty infiltration .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 . However, the sensitivity appears to be decreased in patients who are morbidly obese . 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 .

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 .
- 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)

CT, MRI, and magnetic resonance spectroscopy

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

- 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

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** .
- 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.

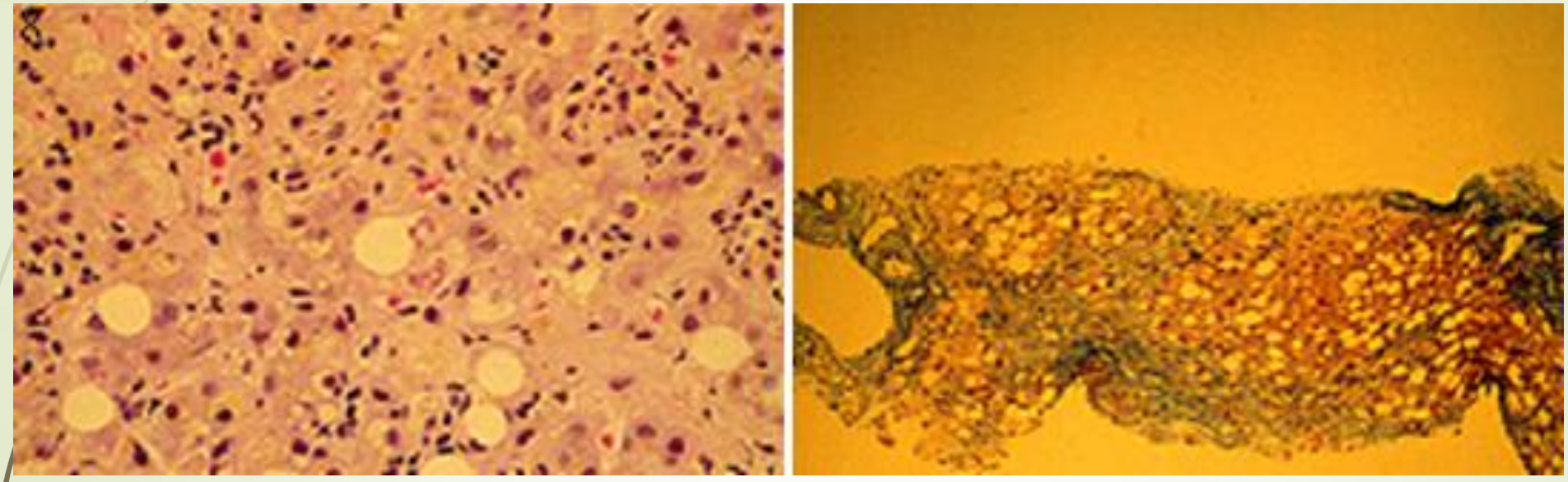
Which patients to biopsy

- There is no clear consensus about which patients require a liver biopsy
- . 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.

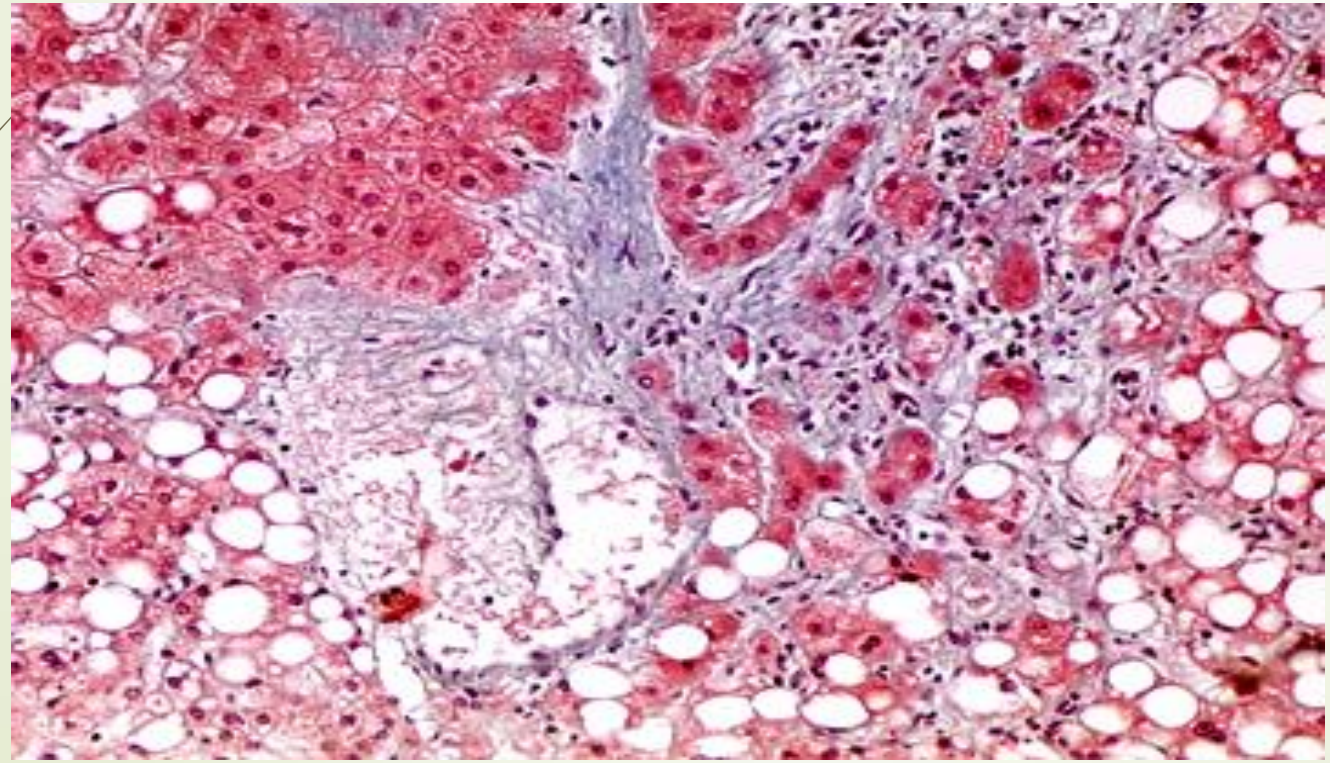
Specifically, we obtain a biopsy if the patient:

- ●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 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.



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



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 :
- ●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 . 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 .

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

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. 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.


Thank you