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Nonalcoholic Fatty Liver Disease

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Nonalcoholic fatty liver disease (NAFLD) refers to the accumulation of fat (mainly triglycerides) in hepatocytes resulting from insulin resistance. NAFLD is recognized as the most common chronic liver disease in the Western world. It encompasses a wide spectrum of disease from bland hepatic steatosis, which is generally benign, to nonalcoholic steatohepatitis (NASH), which may progress to cirrhosis and liver failure. Hence, distinguishing between hepatic steatosis and NASH has important prognostic and management implications.

NAFLD may be categorized as primary or secondary depending on the underlying pathogenesis. Primary NAFLD occurs most commonly and is associated with insulin-resistant states such as obesity, type II diabetes, and dyslipidemia. Other conditions associated with insulin resistance, such as polycystic ovarian syndrome and hypopituitarism, have also been described in association with NAFLD, although the exact prevalence and significance in these conditions remains unclear. Distinction from secondary types is important as these have different treatment and prognosis. Primary NAFLD has reached epidemic proportions in many countries around the world as demonstrated in several population-based studies. In the United States, 34% of the population aged 30-65 years and 9.6% of the population aged 2-19 years has hepatic steatosis. The prevalence of NAFLD in the general population is higher than the prevalence of hepatitis C virus (HCV) infection and alcohol-induced liver disease. However, this high prevalence of NAFLD contrasts with the relatively small proportion of individuals with NAFLD who will show evidence of disease progression or who will develop complications of end-stage liver disease.

Patients may complain of fatigue or malaise and report a sensation of fullness or discomfort in the right upper abdomen. Hepatomegaly and acanthosis nigricans are common physical findings in children, although stigmata of chronic liver disease suggestive of cirrhosis are uncommon. The impact of NAFLD on health-related quality of life is being currently evaluated. Several studies have found a significant detrimental impact on health-related quality of life from the several comorbidities constituting the metabolic syndrome, which often cluster with NAFLD. The most common clinical scenario leading to diagnosis of NAFLD is an asymptomatic elevation of serum aminotransferase (ALT, AST) levels not due to viral hepatitis, iron overload, or alcohol abuse. NAFLD should also be considered as a possible differential diagnosis among patients with "cryptogenic" cirrhosis. The prevalence of metabolic risk factors such as diabetes and obesity is similar amongst patients with cryptogenic cirrhosis and NASH. In addition, prevalence rates of these risk factors are higher when compared with patients with cirrhosis resulting from other etiologies, suggesting NASH accounts for a substantial proportion of cases of cryptogenic cirrhosis.

The most common comorbid conditions associated with NAFLD are metabolic syndrome components. The metabolic syndrome is defined as three or more of the following: fasting glucose ≥ 100 mg/dL, central obesity with waist circumference > 102 cm (40 inches) in men and > 88 cm (35 inches) in women, blood pressure $\geq 130/85$ mmHg, fasting triglyceride level ≥ 150 mg/dL, and low HDL cholesterol (< 40 mg/dL in men, < 50 mg/dL in women). About 90% of NAFLD

patients have a body mass index (BMI) ≥ 25 kg/m². Obesity (BMI ≥ 30 kg/m²) is present in 50% of the patients with NAFLD, type 2 diabetes in 28%, dyslipidemia (either hypertriglyceridemia, hypercholesterolemia, or low HDL-cholesterol alone or in combination) in 55%, and hypertension in 60%, and almost 50% of the patients with NAFLD suffer from the metabolic syndrome, *i.e.*, they show at least 3 features of the metabolic syndrome.

Also, about 75% of lean patients (BMI < 25 kg/m²) with NAFLD have at least one feature of the metabolic syndrome. Therefore, the presence of metabolic abnormalities increases the likelihood of NAFLD; however, these features are common in the general population and not specific for the diagnosis. As about biochemical features, serum liver enzyme abnormalities are often restricted to elevations of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST), and usually at levels below five-fold normal levels. Aminotransferase levels among NAFLD patients fluctuate with normal levels present in up to 78% of patients at any time point, but found elevated in more than 20% of these patients if repeated at several points during the follow-up. Alkaline phosphatase and γ -glutamyl transferase levels may be modestly elevated (generally less than 3 times normal) in a third of cases but are rarely elevated in isolation. Hyperbilirubinemia, low albumin levels, or increased international normalized ratio (INR) usually indicate decompensated cirrhosis. Serum iron tests are commonly abnormal; elevated ferritin levels are found in up to 50% of patients and transferrin saturation is increased in up to 10% of cases. These findings may potentially lead to confusion regarding hemochromatosis diagnosis. Whether there is an increased prevalence of heterozygous HFE gene mutations among patients with NAFLD is controversial; however, their presence does not appear to be associated with hepatic iron loading or liver fibrosis. Testing for antinuclear and/or antismooth muscle antibodies in patients with chronically elevated enzymes to screen for autoimmune hepatitis is recommended. However serum autoantibodies are present in 23% to 36% of NAFLD patients and may rarely signal coexistent autoimmune liver disease. In one series of 225 NAFLD patients, 8% of autoantibody-positive patients also had coexistent features of autoimmune hepatitis on liver biopsy. Liver biopsy features help to exclude the diagnosis of autoimmune hepatitis

in the vast majority of patients with NAFLD who are antinuclear and/or antismooth muscle antibodies positive.

Ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) can noninvasively diagnose fatty infiltration of the liver. Hepatic steatosis causes increased echogenicity on ultrasound, which can be contrasted against the lower echogenicity of the spleen or renal cortex. A similar pattern can be seen in diffuse fibrosis, giving rise to the term “fatty-fibrotic pattern,” although the echo shadows tend to be coarser in the presence of pure fibrosis. The sensitivity and specificity of ultrasound for detecting hepatic steatosis range from 60% to 94% and 88% to 95%, respectively. However, the sensitivity of ultrasound decreases with lower degrees of fatty infiltration. In the presence of $\geq 30\%$ fatty infiltration, the sensitivity of ultrasound is 80% compared with a sensitivity of 55% when hepatic fat content is 10%-19%. Similarly, in the presence of morbid obesity the sensitivity and specificity of ultrasound decrease to 49% and 75%, respectively.

On noncontrast images by CT scan, hepatic steatosis has a low attenuation and appears darker than the spleen. The sensitivity of CT at detecting greater than 33% hepatic steatosis is up to 93%, with a positive predictive value of 76%. Both magnetic resonance phase contrast imaging techniques and magnetic resonance spectroscopy are reliable at detecting steatosis and offer good correlation with hepatic fat volume. More than 5% of hepatic fat content on magnetic resonance spectroscopy indicates presence of steatosis. However, the routine application of magnetic resonance images is limited by its cost and lack of availability.

NAFLD is histologically indistinguishable from the liver damage resulting from alcohol abuse. Liver biopsy features include steatosis, mixed inflammatory cell infiltration, hepatocyte ballooning and necrosis, glycogen nuclei, Mallory's hyaline, and fibrosis. The presence of steatosis alone or in combination with the other features, accounts for the wide spectrum of NAFLD. Steatosis is present predominantly as macrovesicular fat, although some hepatocytes may show an admixture with microvesicular steatosis. When mild, fatty infiltration is typically concentrated in acinar zone 3, whereas moderate to severe fatty infiltration shows a more diffuse distribution. The inflammatory infiltrate usually consists of mixed

neutrophils and lymphocytes and predominates in zone 3. Ballooning degeneration of hepatocytes results from intracellular fluid accumulation and is characterized by swollen cells typically noted in zone 3 near the steatotic hepatocytes. Mallory's hyaline is found in about half of adult patients with NAFLD and is usually located in ballooned hepatocytes in zone 3, but it is neither unique nor specific for NAFLD. The pattern of fibrosis is one of the characteristic features of NAFLD. Collagen is first laid down in the pericellular space around the central vein, and in the perisinusoidal region in zone 3. In some areas, the collagen surrounds single cells in a pattern referred as "chicken-wire" fibrosis as described in alcohol-induced liver damage. This pattern of fibrosis helps to distinguish NAFLD and alcoholic liver disease from other forms of liver disease in which fibrosis shows an initial portal distribution.

Portal tracts are relatively spared from inflammation, although children with NAFLD may show a predominance of portal-based injury as opposed to a lobular pericentral injury. Mallory's hyaline is notably sparse or absent in children with NAFLD. In some patients with cirrhotic stage, the features of steatosis and necroinflammatory activity may no longer be present.

The histologic distinction between hepatic steatosis and NASH with high-grade inflammation and fibrosis is relatively clear; however, differentiating more subtle changes in the middle of the spectrum may be difficult. Furthermore, different histological definitions have been used to categorize NASH. The most accepted one requires the presence of zone 3 accentuated macrovesicular steatosis in conjunction with mild mixed lobular inflammation and hepatocellular ballooning. Although liver biopsy is the gold standard for diagnosing NASH and staging fibrosis, sampling variability may underestimate the severity of liver injury.

The gold standard for diagnosing NAFLD is clinicopathologic correlation, based on confirmation of steatosis by liver biopsy and appropriate exclusion of other etiologies. It is important to exclude alcohol abuse as the cause of fatty liver. It is known that a minimal amount of alcohol of 20 g/day (1-2 standard drinks) in women and 30 g/day (2-3 standard drinks) in men can induce fatty liver; these limits are commonly used to distinguish between alcoholic and nonalcoholic fatty

liver. Secondary causes of NAFLD such as medications (eg, prednisolone, tamoxifen, amiodarone, methotrexate), total parenteral nutrition, cachexia, intestinal bypass surgery, human immunodeficiency virus, and lipodystrophy should be excluded as NAFLD associated with such conditions has a different course and treatment.

The potential benefits of liver biopsy must be weighed against the small risk of complications, including pain, bleeding, and death. The decision to pursue biopsy needs to be discussed and individualized with each patient. A number of clinical and laboratory features are recognized in association with NASH and/or advanced fibrosis in patients with NAFLD including older age, presence of diabetes, higher BMI, higher AST/ALT ratio, and low albumin and platelet count. These features have been combined in a numerical score aimed at predicting the presence or absence of advanced fibrosis in NAFLD. More recently, advanced fibrosis among NAFLD patients has been associated with levels of novel serum markers of fibrogenesis, including hyaluronic acid, propeptide of type III collagen, and tissue inhibitor of matrix metalloproteinase-1. These serum markers have been combined in a numerical score named the Enhanced Liver Fibrosis panel to predict the presence and severity of liver fibrosis in NAFLD. Similarly, the Fibrotest which has been extensively studied in viral hepatitis to predict severity of fibrosis has been evaluated in NAFLD. In addition, caspase-3-generated cytokeratin (CK)-18 fragments, a marker of apoptosis measured in plasma, has been evaluated in distinguishing simple steatosis from NASH. Using plasma from 44 patients with NAFLD, the authors reported a specificity of 99.9%, a sensitivity of 85.7%, and positive and negative predictive values of 99.9% and 85.7% respectively of a value of CK-18 of 395 U/L for the diagnosis of NASH. Although all of these scores based on laboratory markers aid in the decision regarding who should be biopsied, further validation is required before they can be routinely used in clinical practice.

Knowledge of the histologic subtype of NAFLD and stage of fibrosis is useful to guide prognosis and may alter clinical management. The natural history of uncomplicated hepatic steatosis is relatively benign, with follow-up of 239 patients for an average of 12 years demonstrating progression to cirrhosis in 3 (1.3%) patients and liver-related death in only 2 cases (0.8%). In contrast, up to

15% of patients with NASH may progress to cirrhosis within 15 years of diagnosis. Therefore, a diagnosis of NASH may prompt a more aggressive therapeutic approach toward metabolic risk factors and novel agents' clinical trials participation, if available. The presence of advanced fibrosis or cirrhosis should prompt screening for hepatocellular carcinoma and esophageal varices with closer monitoring for disease-related complications. Histologic staging is also valuable for tracking disease progression and monitoring response to therapy. However, it is important to keep in mind that changes in aminotransferase levels do not reliably correlate with histologic changes over time.

A large body of clinical and epidemiological data gathered during the last three decades indicates that obesity, type 2 diabetes mellitus and hyperlipidemia are major associated conditions or predisposing factors leading to the development of NAFLD. Hence, it is reasonable to believe that the prevention or appropriate management of these conditions would lead to improvement or arrest of the liver disease. Weight loss, particularly if gradual may lead to improvement in liver histology in NAFLD. However, rate and degree of weight loss required for normalization of liver histology have not been established. Total starvation or very low calorie diets may cause worsening of liver histology and thus should be avoided. The National Heart, Lung and Blood Institute and National Institute of Diabetes and Digestive and Kidney Diseases expert panel clinical guidelines for weight loss recommend that the initial target for weight loss should be 10% of baseline weight within a period of 6 months. This can be achieved by losing about 0.45 to 0.90 kg (1-2 lb) per week. If successful, further weight loss can be attempted should that be indicated through further assessment. The panel recommends weight loss using multiple interventions and strategies, including lifestyle modification (*i.e.*, diet modifications, increased physical activity), behavioral therapy, pharmacotherapy (*i.e.*, orlistat, phentermine, sibutramine), and surgery, as well as through a combination of these treatment modalities. The recommendation for a particular treatment modality or combination should be individualized considering the BMI and the presence of concomitant risk factors and other diseases. The panel has not made specific recommendations for the subgroup of patients with NAFLD; however, given the lack of clinical trials in this area, the

overall panel recommendations may be a useful and safe first step for obese patients with NAFLD. Similarly, no specific recommendations for liver tests monitoring during weight loss were made, but measuring liver enzymes monthly during weight loss seems appropriate.

Different dietary energy restrictions have been used. However, further studies are necessary to determine the most appropriate content of the formula to be recommended for obese and/or diabetic patients with NAFLD. In the absence of well-controlled clinical trials in patients with NAFLD, it may be tempting to suggest a heart-healthy diet as recommended by the American Heart Association for those without diabetes, and a diabetic diet as recommended by the American Diabetes Association for those with diabetes. Dietary supplementation with n-3 polyunsaturated and monounsaturated fatty acids may improve insulin sensitivity and prevent liver damage. Saturated fatty acids worsen insulin resistance whereas dietary fiber can improve it. Nevertheless, the effect of such a dietary modifications in patients with fatty liver remains to be established. Diets to reduce weight should always be prescribed on an individual basis and considering the patient's overall health. Patients with obesity-related diseases such as diabetes mellitus, hyperlipidemia or cardiovascular disease will require close medical supervision during weight loss to adjust the medication dosage as needed.

Improving insulin sensitivity with lifestyle changes or medications usually improves glucose and lipid levels in patients with diabetes and hyperlipidemia. Improving insulin sensitivity in these patients is expected to improve liver disease, but in many diabetic/hyperlipidemic patients with NAFLD, the appropriate control of glucose and lipid levels is not always accompanied by improvement of the liver condition.

Based on the fact that achieving and maintaining appropriate weight control is a difficult task to accomplish by most obese patients, the use of medications that can directly reduce the severity of liver damage independent of weight loss is a reasonable alternative. Pharmacological therapy may also benefit patients lacking risk factors or associated conditions such as non-obese, non-diabetic patients and those with a normal lipid profile. However, pharmacological therapy directed specifically at the liver disease has only recently

been evaluated in patients with NAFLD. Most of these studies have been uncontrolled, open-label and have lasted one year or less and only few of them have evaluated the effect of treatment on liver histology. Results of pilot studies evaluating insulin sensitizer medications, antioxidants, lipid-lowering medications, and some hepatoprotective medications suggest that these drugs may be of potential benefit, but well-designed controlled trials are needed before any of them can be recommended for patients with NAFLD.

■ General recommendations

An attempt at gradual weight loss is a useful first step in the management of patients with NAFLD as is making a concerted effort to maintain appropriate control of serum glucose and lipid levels. Perhaps along with appropriate exclusion of other liver diseases, this may be the only treatment recommendation for patients with pure steatosis and no evidence of necroinflammation or fibrosis who seem to have the best prognosis within the spectrum of NAFLD. Patients with steatohepatitis, particularly those with increased fibrosis on liver biopsy may have a worse prognosis and should be monitored closely, making a greater effort for adequate metabolic control, and be offered enrollment in well-controlled clinical trials evaluating the potential benefit of promising medications. Pharmacological therapy holds promise, but data from well-controlled clinical trials are still needed to determine not only the medications efficacy but also their long-term safety. At present, none of these medications can be recommended for the treatment of NAFLD outside of those patients with cirrhotic stage NAFLD and decompensated disease, liver transplantation is a potential life-extending therapeutic alternative although some

cirrhotic patients with NAFLD suffer from comorbid conditions that often reduce the usefulness of liver transplantation.

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