Nonalcoholic Fatty Liver Disease and Metabolic Syndrome

Pipop Jirapinyo, M.D.

Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol Univesity, Bangkok 10700, Thailand.

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Nonalcoholic fatty liver disease (NAFLD) is a condition characterized by significant lipid deposition greater than 5% of the liver weight without any history of excessive alcohol intake. Now it refers to a spectrum of diseases of the liver ranging from steatosis fatty infiltration of the liver to NASH (steatosis with inflammation and hepatocyte necrosis. It is the most common cause of elevated liver enzymes in adults in the United States.[1] The prevalence of NAFLD ranges from 20% to 30% in the Western Population. The prevalence is higher in patients who have metabolic syndrome and in patients with insulin resistance. NAFLD is now recognized as an important childhood liver disease and is likely to reach epidemic proportions in children worldwide in the next decade.[2] Metabolic syndrome is currently very commonly found both in obese adults and obese children. NAFLD now is a common feature of the metabolic syndrome.

Definition and Classification

NAFLD is considered when there is fat deposition more than 5% of the hepatocytes. It is classified into 4 classes

Class I simple hepatosteatosis
Class II increased hepatosteatosis with or without NASH*
Class III increased hepatosteatosis with NASH*
Class IV increased hepatosteatosis with increased NASH*

*NASH - nonalcoholic steatohepatitis

Generally, NAFLD is associated with obesity, hyperlipidemia and insulin resistance. This close association suggests pos-sible links between these disorders. On this basis, NAFLD has been included as part of the metabolic syndrome. However, NAFLD can also occur in non-obese/non-diabetic patients as well as in patients with lipodystrophy.

Clinical course[3]

Simple forms of NAFLD are characterized by triglyceride accumulation in hepatocytes. This frequently is complicated by inflammation (NASH). NAFLD may progress to hepatitis, cirrhosis and to hepatocellular carcinoma. Simple steatosis may develop into NASH in one third of cases. A considerable subset (up to 50%) of NASH patients can develop fibrosis and about 15% to 19% develop cirrhosis. The risk of malignant complication in these patients is increased more than 4 times.

Diagnosis[4]

NAFLD is essentially an asymptomatic condition. The diagnosis is usually made when liver aminotransferase (ALT) and/or aspartate aminotransferase (AST) enzymes are elevated or when there is ultrasonographic or radiological evident of fatty liver. Table 1 lists the more common causes of elevated liver enzymes. Fig 1 shows pathways to diagnose NAFLD.[5]

The diagnosis of NAFLD requires exclusion of alcoholic liver disease and viral hepatitis. The American Gastroenterological Association recommends that patients with suspected NAFLD be questioned carefully about alcohol use.

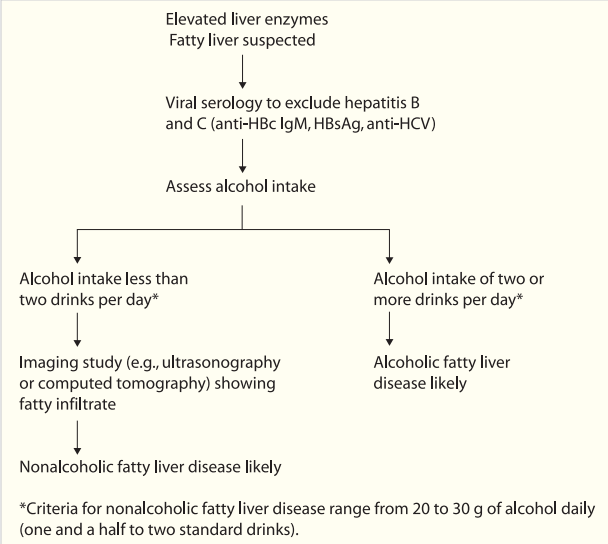


Fig 1. Diagnosis of Fatty Liver Diseases.

TABLE 1. Differential diagnosis of elevated liver transaminase levels.

Diagnosis	Steatosis present?	Alcohol abuse?	History	Physical findings
Fatty liver	Yes	No	Type 2 diabetes, increased body mass index, hyperlipidemia	Obesity, often asymptomatic
Alcohol	Yes	Yes	Alcohol use > 20 to 30 g per day (1.5 to 2 standard drinks)	Hepatomegaly, right upper quadrant tenderness
Autoimmune	No	No*	Type 1 diabetes, Graves' Disease, ulcerative colitis, vasculitis, Sjogren's disease	Increased incidence in women (4:1)
Viral hepatitis	No†	No*	Risk factors: illicit injection drug use, risky sexual behaviors, transfusions	Right upper quadrant tenderness, jaundice
Medication induced	Yes	No*	Increased transaminase levels after starting medication, resolves upon discontinuation	Variable
Hemochromatosis	No	No*	Family history	Increased skin pigmentation, hepatomegaly, testicular atrophy, decreased libido, fatigue, cardiomyopathy

Note: Not all patients will have all of these findings.
*— Not necessary for the diagnosis, but may worsen toxicity.
†— Steatosis is present with hepatitis C.

The initial laboratory evaluation should include ALT, AST, alkaline phosphatase, serum bilirubin, albumin levels; a prothrombin time; which are diagnostic tests for viral hepatitis.

Imaging studies

Imaging studies assist in the diagnosis of NAFLD through identifying fatty infiltrate in the liver. Ultrasonography of the liver has a sensitivity of 82 to 89 percent and a specificity of 93 percent for identifying fatty liver infiltrate. Computed tomography is no more sensitive than ultrasonography and is more expensive.

Cytokines in NAFLD[6]

Cytokines are key mediators of hepatic inflammation, liver cell death, cholestasis, and fibrosis as well as regeneration of the liver after injury. Production of cytokines such as interleukin-6 (IL-6) and tumor necrosis factor α (TNF α), the 2 prototypic pro-inflammatory cytokines, is one of the earliest events in many types of liver injury, triggering the production of other cytokines that together recruit inflammatory cells and initiate a healing process in the liver that includes fibrogenesis.

Two-hit model

There is a 2-hit hypothesis to explain the development of NASH from NAFLD (Fig 2).[7] The first hit is from the accumulation of free fatty acids in the liver resulting in increasing secretion of adipokines. This event causes insulin resistance from retarded insulin clearance and increased lipid synthesis in the liver. The increased lipid accumulation in the liver has direct cytotoxicity to the parenchymal cells of the liver. The second hit is from the free radicals that occur in the hepatocytes. When mitochondrias are overloaded with fatty acid β-oxidation, there will be increasing peroxisomal fatty acid oxidation which will result in increased H_2O_2 production. The H_2O_2 is a potent oxidative stress to the hepatocytes.

TABLE 2. Diagnosis of metabolic syndrome.

Criteria	Value
Waist circumference	Male ≥ 120 cm Female ≥ 88 cm
Blood pressure	≥ 130/85 mmHg
Fasting glucose	≥ 110 mg/dl
Fasting triglycerides	≥ 150 mg/dl
HDL cholesterol	Male ≤ 40 mg/dl Female ≤ 50 mg/dl

Metabolic syndrome

The National Cholesterol Education Program Adult Treatment Panel III (ATP III) proposes the definition of metabolic syndrome as shown in Table 2. Anyone who fits with 3 of the 5 criteria is considered to have metabolic syndrome. It is shown that improvement of metabolic syndrome results in improvement of NAFLD.

Treatment

Steatosis alone probably does not warrant treatment. Treatment of NASH may be considered, particularly in patients with more advanced disease on biopsy. To date, there are no data that demonstrate improvement in morbidity or mortality rates. Weight loss and exercise have been shown to reduce liver enzyme levels and steatosis in children and adults who are obese. Treatment of insulin resistance has improved disease oriented outcomes in patients with NAFLD. Medications for treating hyperlipidemia also have improved biochemical and histological results in patients with NAFLD.

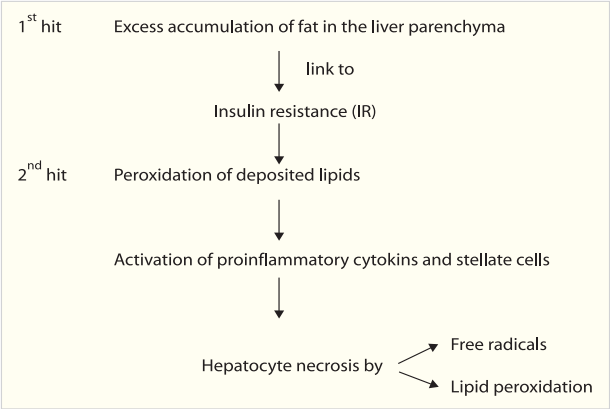


Fig 2. 2-hit model.

Prognosis

The prognosis of NAFLD depends upon the extent of liver damage. Steatosis alone generally has a benign course, and progression to cirrhosis is rare. Although some cases of NASH appear to progress to cirrhosis, data are limited regarding how common that progression is. Risk factors for more severe liver disease include diabetes, increasing weight, older age, and an ASL/ALT ratio of greater than 1.

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