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FATTY LIVER: A LINK TO CARDIOVASCULAR DISEASE – ITS NATURAL HISTORY, PATHOGENESIS, AND TREATMENT

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Abstract

Nonalcoholic fatty liver disease (NAFLD) has become the most prevalent liver disease in western society and is increasing in parallel with the worldwide epidemic of obesity. It exists in a simple form, steatosis, or a more complex and more dangerous form, steatohepatitis, and it is often but not always associated with the metabolic syndrome. NAFLD can progress to cirrhosis and hepatocellular carcinoma. It is responsible for the majority of cryptogenic cirrhosis cases. Increasingly, NAFLD and its more sinister form, steatohepatitis, have been linked to the increased incidence of cardiovascular disease (CVD) worldwide, independent of the metabolic syndrome. Death from CVD surpasses death from liver complications, but that is beginning to change as people are living longer with CVD. In this article, we will review nonalcoholic fatty liver disease and its epidemiology, prevalence, pathology, and link to CVD.

Definition

Nonalcoholic fatty liver (NAFLD) is the most common cause of elevated transaminases. NAFLD exists when, on pathologic review, greater than 5% of liver cells contain fat.[1, 2] It is said to be severe when greater than 30% of liver cells contain fat on biopsy. NAFLD may exist as a simple entity, bland fatty liver (steatosis), or a more complex inflammatory entity, steatohepatitis, also referred to as nonalcoholic steatohepatitis (NASH), which is a pathological diagnosis. On biopsy it consists of steatosis, hepatocyte ballooning degeneration, diffuse lobular mixed acute and chronic inflammation, and perivenular, perisinusoidal collagen disposition.[3] In the schema of progression of fatty liver disease, NAFLD progresses to NASH, which then progresses to cirrhosis and/or hepatocellular carcinoma (Figure 1).

NAFLD is a diagnosis of exclusion (Table I). Excessive alcohol consumption needs to be ruled out; this is important because on biopsy NAFLD or NASH is indistinguishable from alcoholic liver disease. Excess alcohol consumption is defined as more than 30 grams per day for men and more than 20 grams per day for women; 10 grams of alcohol is equal to 12 ounces of beer, 4 ounces of wine, and 1.5 ounces of hard liquor. Viral hepatitis, autoimmune hepatitis, and other metabolic liver diseases also need to be ruled out by various laboratory studies.

Incidence, Prevalence, and Risk Factors

The incidence of NAFLD is underreported. In the United States, it is estimated that the prevalence of fatty liver is approximately 30% of the population.[4] Approximately 3–5% of fatty liver patients have NASH. NASH will progress to cirrhosis in about 20% of the cases. At the time of biopsy, up to one-third of NASH patients have advanced hepatic fibrosis and 10–15% will have established cirrhosis.

1. Alcohol consumption: (M <30 g/d; F <20 g/d)
2. Review medications as possible etiology
3. Exclude other possible causes of elevated transaminases: • HCV: HCV-Ab HBV: HBsAG, HBcAb, HBV-DNA (where appropriate) • AIH: ANA, ASmAb, • Hemochromatosis: FE/TIBC with iron saturation, HFE genes (where appropriate) • Wilson's disease: Ceruloplasmin level • Alph-1 AT Deficiency: Alph-1 AT Level, Pi-Typing (when appropriate)
4. Radiology: US/CT scan with contrast
5. Biochemical evaluation: • Liver Panel • CBC with diff/plt • TSH • Fasting Lipid Panel • 75-g 2-hr GTT (see text) • Fasting: glucose, insulin, proinsulin, and C-Peptide • Other: hs-CRP, uric acid, urine for microalbumin

Table 1. Evaluation of NAFLD.
Legend: AT: antitrypsin; US/CT: ultrasound/computed tomography scan; GTT glucose tolerance test; HFE: human hemochromatosis protein; hs-CRP: high-sensitivity C-reactive protein; HCV: hepatitis C virus; HCV-Ab: hepatitis C virus antibody; HBV: hepatitis B virus; HBsAG: hepatitis B surface antigen; HBcAb: hepatitis B core antibody; HBV-DNA: hepatitis B virus DNA; CBC: complete blood count; TSH: thyroid stimulating hormone; FE/TIBC: iron/total iron-binding capacity

Figure 1. The progression sequence of fatty liver.

Obesity with fatty liver (NAFLD) 30% of population → Steatohepatitis (NASH) 3% to 5% → Cirrhosis 20% → HCC 2.8%

Obesity	Waist: >40 inches (102 cm) in men >35 inches (88 cm) in women
Impaired fasting glucose/ insulin resistance	Fasting blood sugar >100 mg/dL
Hyperlipidemia	Triglyceride: >250 mg/dL HDL: <40 mg/dL men <50 mg/dL women
Hypertension	BP: ≥130/85 mmHg

Table 2. Metabolic syndrome.*
**Defined as ≥3 of these parameters*

Age >45 yrs
Type 2 diabetes
Overweight/obesity: BMI >28
AST/ALT ratio >0.8
Others signs of advanced liver disease

Table 3. When to consider liver biopsy in NAFLD: Predictors of advanced fibrosis.

Affected persons typically present between the fourth and sixth decades of life. Women, in most western studies, are more affected than men, although men may have more progressive disease. If the current upper limit of normal alanine aminotransferase (ALT) activity in women is dropped from 30 U/L to the newly recommended 19 U/L, the incidence in women will double.[5] In the United States there are ethnic differences, with the highest NAFLD prevalence in the Hispanic population (45%) followed by Caucasians (33%) and African Americans (24%).[6]

There appears to be a genetic predisposition for nonalcoholic fatty liver disease as familial clustering has been described.[7-9] Genes have been identified that predispose individuals to nonalcoholic fatty liver disease. Homozygous carriers of a gene allele that encodes adiponutrin, the Il48M allele of the PNPLA3 gene, have been shown to have hepatic fat content more than two-fold higher than noncarriers. This allele is more prevalent in Hispanics, followed by Caucasians and African Americans — similar to the prevalence of NAFLD in the U.S. population.[10] Furthermore, it has been shown that a variant of the same gene, common in African Americans but rare in Europeans and Hispanics, is associated with significantly lower liver fat content. The same gene alleles appear to be strongly correlated with elevated serum levels of ALT, aspartate aminotransferase (AST), and liver inflammation.

Obesity is strongly related to fatty liver disease and occurs in 69–100% of NAFLD cases.[11] NAFLD/NASH is strongly associated with the metabolic syndrome (Table 2).[12] Features of the metabolic syndrome include obesity (waist: >40 inches (102 cm) for men; >35 inches (88 cm) for women), impaired glucose tolerance or diabetes mellitus (fasting blood glucose level ≥100 mg/dL), hyperlipidemia (triglyceride level >250 mg/dL and/or high-density lipoprotein level <40 mg/dL for men and <50 mg/dL for women), and hypertension (≥130/85 mmHg). The metabolic syndrome is diagnosed by the presence of three or more of these parameters. Any patient presenting with one of these features and elevated transaminases should be evaluated for possible NAFLD/NASH. The prevalence of NASH increases in parallel with the number of metabolic syndrome components.

Diagnosis

Most patients with fatty liver disease are asymptomatic, although vague right upper-quadrant pain will occasionally bring the patient to the physician's office. The most common presentation is elevation of liver transaminases. This occurs primarily in the presence of steatohepatitis. The AST/ALT ratio is usually less than 1 unless advanced fibrosis exists.[13] The ratio is almost never greater than 2, which is the ratio most often seen in alcoholic hepatitis, thus the ratio can be used as a distinguishing factor in considering the diagnosis.

Biopsy is the gold standard for diagnosing NAFL, although it is invasive and expensive. It is important to remember that normal aminotransferases do not exclude the presence of advanced disease, thus biopsy should be considered in most patients. Patients may be selected for biopsy depending on certain predictors (Table 3). Predictors of advanced histology include patients 45 years of age and older, obesity, type 2 diabetes, or an AST/ALT ratio greater than 0.8.[14, 15] Clues to advanced liver disease found on physical examination and/or a low platelet count that suggests the possible presence of occult cirrhosis should prompt the physician to consider a biopsy. The biopsy specimen should be at least 2 cm in length and contain 6–11 portal tracts to ensure adequate diagnosis.

Ultrasound, CT scan, and MRI can be used to suggest a diagnosis of fatty liver disease,[16] although no imaging modality is able to differentiate simple fatty liver disease from steatohepatitis. Ultrasound may suggest fatty liver by demonstrating hyperechoic texture but should not be used to make a diagnosis of NAFLD. Ultrasound is unreliable in morbidly obese patients due to technical difficulties. CT and MRI can more readily identify steatosis. A contrast-enhanced CT is better than a noncontrast-enhanced CT, with an 82% sensitivity and 100% specificity in detecting hepatic steatosis >30%.[17] A decrease in hepatic attenuation (1.6 HU for every milligram of triglyceride deposited per gram of liver tissue) in comparison to the surrounding vasculature gives the steatotic liver the appearance of contrast enhancement. Recently, MR spectroscopy has shown promise in the ability to quantify the amount of steatosis in the liver. However, no radiologic modality is able to distinguish steatohepatitis, the strongest predictor of progression to cirrhosis.

Pathogenesis, Natural History, and the Link to Cardiovascular Disease

The pathogenesis of NAFLD is yet to be elucidated. The most excepted theory is that of the "two-hit" hypothesis. The major contributor to the increased deposition of visceral fat and free fatty acids in the liver cells is insulin resistance. Some believe a "second hit" or additional oxidative stress-type injury is required to induce an inflammatory response. It is the inflammatory response that leads to the progression to cirrhosis and the extrahepatic manifestation of coronary artery disease. Obesity itself is characterized by increased storage of fatty acids and an expanded adipose tissue mass. Visceral adipose tissue is a source of a number of secreted proteins and acts as an endocrine organ.[18] Leptin, adiponectin, resistin, and retinol-binding protein 4 are a group of proteins secreted by adipose tissue and collectively

known as adipokines. They interact to play a significant role in whole body metabolism by regulating energy expenditure, inhibiting food intake, restoring euglycemia, increasing insulin sensitivity and fatty acid oxidation, and the production of glucose by the liver. Studies show that their up or down regulation play a central role in the development of the metabolic syndrome. In addition, visceral macrophages have been identified within adipose tissue as the main source of inflammatory cytokines, tumor necrosis factor-alpha (TNF-α), and interleukin-6. Increased levels of macrophage-derived factors in obesity leads to a state of chronic low-grade inflammation. These are the same inflammatory cytokines that have been identified in atherogenesis. This led to the earlier belief that the liver played a passive role in the development of atherosclerosis and coronary vascular disease, merely demonstrating pathologic manifestation of the same general process.

In the past several years, multiple studies have begun to change this way of thinking. The leading cause of death in patients with NAFLD is from coronary events.[19-22] In patients with diabetes mellitus, NAFLD is associated with CVD independent of the classical risk factors, glycemic control, medications, and metabolic syndrome features. When diabetic patients with and without NAFLD are compared, those with NAFLD have a higher prevalence of coronary vascular disease, hypertension, central obesity, poor glycemic control, and dyslipidemia and greater carotid intimal thickness. Furthermore, with the development of steatohepatitis, the degree and severity of CVD becomes directly proportional to the amount of inflammation on liver biopsy. Cardiovascular mortality is also increased at least two-fold in NASH. The presence of liver fat is associated with lower adiponectin levels and increased levels of fibrinogen, C-reactive protein (CRP), and plasminogen activator inhibitor 1 (PAI-1), markers of inflammation and risk factors of coronary vascular disease independent of BMI and intra-abdominal obesity. Studies show that histologic severity of NASH on liver biopsy is correlated with higher concentrations of these inflammatory cytokines and that they exist at significantly higher levels than in overweight nonsteatotic patients with comparable values of visceral adiposity. Multivariate regression analysis shows that NASH predicts plasma inflammatory biomarkers independent of visceral adiposity and other potential confounders.[23] These finding suggest that NASH is not simply a marker of CVD but may also be involved in its pathogenesis. Patients with NAFLD also have significantly higher mean values of intima-media thickness and prevalence of plaques. NAFLD is the strongest variable independently associated with carotid intima-media thickness and with increased risk of atherosclerosis in subjects with metabolic syndrome. Steatosis has been found to be the strongest independent risk predictor of vascular damage, followed by age and blood pressure. Patients with NAFLD and systolic BP ≥130 are 4.7 times more likely to have a positive treadmill test. These studies might suggest that obese patients and patients with metabolic syndrome should have a screening liver scan to identify the presence of steatosis and, in turn, those at higher risk of CVD. Although such a prospective study has not yet been done, this type of evaluation needs to be considered to stem this epidemic.

The natural history of NASH is variable. The best studies looking into this are paired biopsy studies.[24, 25] In general, the studies demonstrate a 25–40% progression rate, and they vary in identifying risk factors for progression. They have included inflammation on the initial biopsy, older age, the presence of diabetes mellitus, higher serum aminotransferase concentrations, and biopsy showing ballooning degeneration and/or fibrosis. NASH and its associated fibrosis has been shown to improve following weight reduction and exercise programs. Studies specifically monitoring patients after bariatric surgery have also shown regression of NASH. Whether this regression would translate into fewer cardiovascular events is unknown.

Hepatocellular Carcinoma and NAFLD/NASH

In the United States, the incidence of hepatocellular carcinoma (HCC) has tripled in the last decade.[26] Cryptogenic cirrhosis accounts for 6.9–50% of HCC.[27] A large proportion of cryptogenic cirrhosis has been associated with a prior history of diabetes, insulin resistance, and obesity, all of which are risk factors for NASH.[28] The overall prevalence of hepatocellular carcinoma in patients with NAFLD is estimated to be between 0–0.5%[29] and the prevalence of HCC in NASH to be between 0–2.8%.[30] Patients who develop hepatocellular carcinoma in the setting of NASH tend to develop it about 10–15 years later than their counterparts with viral hepatitis and tend to present with larger, more well-differentiated tumors.[31]

In patients with NASH, the presence of obesity, diabetes, iron deposition, age, and advanced fibrosis significantly increases the risk of progression to cirrhosis and subsequent hepatocellular carcinoma development.[32] Large population-based studies have demonstrated an increased risk of hepatocellular carcinoma in patients with diabetes, ranging from 1.8 to a four-fold increase.[33] Interestingly, there is a risk reduction of 25–40% for the development of hepatocellular carcinoma in diabetic patients who were prescribed statins.[34]

Evaluation and Treatment (Table 4)

The association of insulin resistance with fatty liver has long been known but largely ignored since patients with diabetes were more likely to die from CVD before ever progressing to cirrhosis and liver failure. However, with the introduction of more tolerable glucose-lowering therapies, early diagnosis and aggressive management of not just diabetes but also prediabetes (insulin resistance) has become the standard of care. The changing focus from clinical care to primary prevention of not just CVD but also prediabetes has led to earlier initiation of therapy, with the resulting recognition that many of these patients with metabolic syndrome have abnormal liver enzymes. While these liver abnormalities were initially thought to result from therapy such as statins and metformin, we now know that many of them are due to unrecognized extensive fatty liver disease. When one evaluates patients with fatty liver disease, those who do not yet have a diagnosis of type 2 diabetes typically have signs of insulin resistance, with high triglycerides, low HDL, central obesity, and elevated blood pressure. Comprehensive evaluation of an individual suspected of having a fatty liver thus requires not only consideration of liver inflammation and cirrhosis but also evaluation and treatment of each metabolic syndrome component and of possible insulin resistance if diabetes has not yet occurred.

In addition to a fasting lipid profile, evaluation of these patients should include metabolic markers such as hs-CRP, uric acid, urine for microalbumin, fasting glucose, fasting insulin, fasting pro-insulin, and fasting C-peptide. A 75-gram, 2-hour oral glucose tolerance test (GTT) should be performed since many patients with fatty liver will have hyperinsulinemia and impaired glucose tolerance. If the GTT is done with glucose and insulin measured every 30 minutes, one can plot the initial response to the glucose and how quickly they return to normal as indicators of risk of progression to diabetes.[35]

Lifestyle Modification/Weight Reduction
1. Diet • If diabetic: ADA diet • If insulin resistant: low carbohydrate, low fat, avoid fructose soft drinks
2. Exercise program • After cardiac clearance: 105 to 200 min/wk with at least 75 min/wk vigorous exercise
3. Smoking cessation
4. Avoidance of alcohol and other potential hepatotoxins
Non-pharmacological Treatment
1. Vitamin E: 400–800 IU/d
2. Folic acid: 1 mg/d
3. Vitamin C: (optional)
4. Fish Oil
Pharmacological Treatment
1. Insulin sensitizers: pioglitazone
2. Lipid: concentrated fish oil, fibrates, statins
3. Hypertension: angiotensin receptor blockers
4. Other: pentoxifylline, ursodeoxycholic acid

Table 4. Methodist Liver Center: Treatment of NAFLD/NASH

Therapy needs to be directed to all the components of metabolic syndrome, including the underlying insulin resistance. Weight loss is the cornerstone of therapy. The initial recommendation is lifestyle modification with the avoidance of processed sugars and saturated fats. An exercise program is recommended since vigorous exercise (greater than 75 minutes per week) has been shown to decrease the likelihood of having NASH.[36] An exercise tolerance test should be performed first in patients at high risk for CVD. Vitamin E has been shown to significantly improve histology, but some concerns have been raised about a possible increase in all-cause mortality when used as a health supplement. Thiazolidinediones (TZD), a class of insulin sensitizers, have been shown to improve hepatic fat content, inflammation, and fibrosis.[37] Both therapies should be considered. Metformin has been shown to improve fatty liver volume in mice but to have no impact on hepatic histology in humans, thus it is not recommended.[38] Pentoxifylline, a TNF-α inhibitor, has been shown to improve liver histology including fibrosis.[39] Lipids should be brought into target as per NCEP guidelines.[40] There should not be concerns about using statins in patients with fatty liver disease as long as proper monitoring is performed. Statins improve fatty liver and may have an antineoplastic effect. Lowering of triglycerides and non-HDL cholesterol is often necessary using any combination of fibrates, extended release niacin, or concentrated fish oil. Antihypertensive therapy should include RAAS modification, preferentially using the angiotensin receptor blockers (ARB) as these have been demonstrated to positively affect insulin resistance and hepatic fibrosis. Treatment of blood pressure with RAAS modification and aldosterone inhibition is also recommended to avoid the metabolic side effects of most beta blockers and diuretics.

Conclusion

In summary, despite our best treatment efforts, we have yet to identify specific treatment algorithms, and each institution has varied approaches. It must be remembered that the best study results to date have shown statistically significant improvement in histology and fibrosis in less than half the patients studied. Combination therapies targeting individualized treatments and newer pharmacological treatment algorithms are necessary for tackling this century's newest health epidemic.

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