Nonalcoholic Fatty Liver Disease: Review

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Abstract:

Nonalcoholic fatty liver disease (NAFLD) may be the most common liver disease in the world, with a high prevalence in the obese, type 2 diabetic populations, and it is probably underestimated as a cause for cirrhosis. Clinico-pathologically, it represents a wide spectrum of histologic abnormalities and clinical outcomes, ranging from benign hepatic steatosis to cirrhosis. Pathophysiologically, insulin resistance is thought to be pivotal in the development of steatosis, after which a second oxidative stressor produces lipid peroxidation and nonalcoholic steatohepatitis (NASH). Liver biopsy is the gold standard for diagnosis and prognosis. The need for an effective treatment is both clear and urgent, yet in the absence of proven therapies, treatment is directed toward weight loss and comorbidity management. For patients with NAFLD at risk of disease progression, there is a lack of large, randomized, placebo-controlled trials of adequate treatment duration, with baseline stratification according to histologic severity.

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Introduction:

Nonalcoholic fatty liver disease (NAFLD) represents a spectrum of liver disease encompassing simple fatty infiltration (steatosis), fat and inflammation (non alcoholic steatohepatitis (NASH)), and cirrhosis, in the absence of excessive alcohol consumption (typically a threshold of <20 g a day for women and <30 g a day for men is adopted). Simple steatosis has not been associated with liver related morbidity, but NASH may lead to progressive liver fibrosis, cirrhosis and liver cancer, as well as increase cardiovascular risk. NAFLD is strongly associated with obesity, insulin resistance or type 2 diabetes mellitus and dyslipidemia and may be considered the hepatic manifestation of the metabolic syndrome.[1, 2] Significant research endeavors are being directed toward understanding the pathogenesis of NAFLD and designing therapeutic strategies. This article provides a clinical overview of NAFLD, focusing on its epidemiology, etiopathogenesis, diagnosis and treatment.

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Epidemiology:

Estimates vary between populations, but one large European study found NAFLD in 94% of obese patients (body mass index >30), 67% of overweight patients (>25), and 25% of normal weight patients.[3] The overall prevalence of NAFLD in people with type 2 diabetes ranges from 40% to 70%.[3] Asian studies reveal NASH and NAFLD at lower body mass indexes (BMI).[4,5,6] NAFLD probably is the most common liver disorder in the world, affecting 2.8% to 24% of the general population, [7-10] including overweight children and adolescents.[11]Most case of NAFLD occur in the fourth to sixth decades of life. In early clinical studies, a majority of patients with NAFLD were female. In more recent studies, 50% of patients are females.

Etiology:

Many different agents and conditions have been associated with NAFLD. Potential causes of NAFLD are listed in Table-I.

Table-I

Causes of nonalcoholic fatty liver disease:

A. Acquired insulin resistance:
- Obesity
- Diabetes mellitus
- Hyperlipidemia
- Hypothalamic-pituitary dysfunction

B. Drugs and Toxins:
- Amiodarone
- Methotrexate
- Tamoxifen
- Glucocorticoids
- Calcium channel blockers
- Phosphorus
- Organic solvents
- Estrogen

C. Surgical:
- Jejunoileal bypass
- Gastric bypass
- Biliopancreatic diversion
- Extensive small bowel resection

D. Nutritional:
- Total parenteral nutrition
- Starvation and cachexia
- Protein calorie malnutrition: marasmus and kwashiorkor
- Inflammatory bowel disease
- Jejunal diverticulosis with bacterial overgrowth

E. Genetic/inborn errors of metabolism:
- Abetalipoproteinemia
- Galactosemia
- Tyrosinemia
- Wilson's disease
- Glycogen storage disease
- Weber-Christian disease
- Systemic carnitine deficiency

Insulin resistance represents the most important risk factor for the development of NAFLD. Because insulin resistance is also the hallmark of the metabolic syndrome, it is not surprising that there is a close connection between NAFLD and the metabolic syndrome. Indeed, steatosis may simply characterize the hepatic manifestation of the metabolic syndrome. There is also a close association of NAFLD with obesity. The prevalence of obesity in patients with NAFLD is reported to vary from 30% to100%. In obese patients BMI>30 the risk of NAFLD is elevated 4.6 fold.[11]

Pathogenesis:

Although the exact pathogenesis of NAFLD remains poorly understood, the prevailing hypothesis by experts in the field is that several insults or "hits" are involved in causing progressive liver injury.[12] Two hit hypothesis states that dysregulation of fatty acid metabolism leads to steatosis, which is the first hepatic insult in NAFLD. Steatosis is associated with several cellular adaptations and altered signaling pathways, which render hepatocytes vulnerable to "second hit." The second insult may be one or more environmental or genetic perturbations, which cause hepatocyte necrosis and inflammation and activate the fibrogenic cascade, thereby leading to fibrosis and cirrhosis in a minority of patients with NAFLD.

Hepatic steatosis is the hallmark histologic feature of NAFLD. Normally free fatty acids (FFAs) are supplied to the liver through gut absorption (in the form of chylomicron remnants) or from lipolysis of adipose tissue, where FFAs are stored as triglycerides. In the liver, FFAs are oxidized by mitochondria, esterified into triglycerides, synthesized into phospholipids and cholesterol esters, and secreted from the liver as very low density lipoproteins (VLDL). Hepatic triglycerides accumulation occurs when fatty acid metabolism shifts to favor net lipogenesis rather than lipolysis. This shift occurs when the amount of FFA supplied to the liver from the intestine or adipose tissue exceeds the amount needed for mitochondrial oxidation, phospholipid synthesis and synthesis of cholesterol esters. Triglyceride also accumulates in the liver when synthesis of lipoprotein decrease or export of lipids from the liver is impeded.

Current evidence points to insulin resistance and hyperinsulinemia as the primary pathogenic factors in steatosis in most with NAFLD. Diabetes and obesity are associated with increased amounts of FFA in plasma, caused in part by abnormal release of FFA by insulin-resistant adipocytes. Excess FFA contributes to hepatic insulin resistance by down-regulating insulin receptor substrate-1 (IRS-1) signaling. [13] Insulin resistance and hyperinsulinemia lead to steatosis by means of a number of aberrant mechanisms of FFA disposal. In the liver,

insulin stimulates fatty acid synthesis, down-regulates mitochondrial â-oxidation of FFA, blocks the secretion of triglycerides from hepatocytes by increasing intracellular degradation of VLDL and apolipoprotein B-100 (apoB-100), and blocks exocytosis of VLDL-containing vesicles. [14-16] Also, patients with NASH have impaired hepatic synthesis of apoB-100, which also may contribute to hepatic triglyceride accumulation. [17]

Insulin resistance in NAFLD may be potentiated by aberrant levels or function of several important peptide mediators secreted by adipocytes, including TNF-á, leptin, and adiponectin. Adipocytokines are peptides produced by visceral adipose tissue. Adiponectin is secreted by adipocytes in inverse proportion to BMI and is a potent inhibitor of TNF-á. Serum adiponectin levels are reduced in obesity, insulin resistance, diabetes mellitus, and the metabolic syndrome. [18] Delivery of recombinant adiponectin to mice fed a high-fat, alcohol-containing diet and to genetically obese (ob/ob) mice dramatically alleviates hepatomegaly, steatosis, inflammation, and elevated liver biochemical test levels in both murine populations.[19]

Leptin is a satiety hormone, derived from adipocytes, that controls food intake and energy regulation. Leptin is intimately involved with insulin signaling and regulation of glucose metabolism in peripheral tissues and may play an important role in regulating the partitioning of fat between mitochondrial â-oxidation and triglyceride synthesis in the liver. [20] Severe steatosis and steatohepatitis develop in leptin-deficient (ob/ob) mice. Obesity in humans is associated with relative leptin resistance and high leptin levels, which may contribute to the genesis of steatosis by a negative impact on insulin signaling or may be a consequence of the chronic hyperinsulinemia associated with obesity.

Increased levels of FFA can be directly toxic to hepatocytes through a number of mechanisms. An increased FFA concentration leads to lysosomal destabilization and stimulation of TNF-á. [21] FFA also up-regulates cytochrome P450 isoenzymes, leading to enhanced generation of ROS and lipid peroxidation. [22]An increased intracellular FFA concentration can lead to sustained up-regulation of peroxisomal proliferator-activated receptor-á (PPAR-á), which promotes fatty acid oxidation and disposal but also may increase oxidative stress through the production of dicarboxylic acid derivatives; PPAR-á also may predispose affected persons to carcinogenesis.[23] FFA can be directly toxic to cellular membranes, lead to the formation of toxic fatty acid ethyl ethers, and cause overall disruption of mitochondrial function, thereby overwhelming the overlapping protective mechanisms designed to combat FFA hepatotoxicity.[7]

Fibrosis is a frequent histologic finding in advanced NAFLD but has not been well studied in this disease. Hepatic fibrosis results from activation and proliferation of hepatic stellate cells in the subendothelial space of Disse, with subsequent secretion of extracellular matrix components, including collagen types I and III. Factors proposed to initiate and perpetuate the fibrogenic process in stellate cells include inflammatory cytokines, angiotensin, alterations in the extracellular matrix, growth factors, and oxidative stress. In NAFLD, lipid peroxidation products may enhance hepatic production of transforming growth factor-â (TGF-â), which activates stellate cells.[24] Endothelial cells, leukocytes, and Kupffer cells may stimulate the stellate cells to proliferate, possibly through the release of platelet-derived growth factor (PDGF), TGF-â, and other cytokines.[25] In addition, hyperinsulinemia and hyperglycemia associated with NAFLD may stimulate release of connective tissue growth factor, an intermediate molecule involved in fibrogenesis.[26] Finally, animal data suggest that leptin may perpetuate fibrogenesis in NAFLD by stimulating Kupffer cells and sinusoidal endothelial cells to produce TGF-â.[27]

The 'two hit' model of NASH pathogenesis, suggested that the first 'hit' is the development of steatosis sensitizing the liver to the second 'hit'-oxidative stress and cytokines-leading to the development of necroinflammation and ultimately fibrosis and cirrhosis[28].This hypothesis has been challenged by recent data suggesting that mechanisms that can drive disease progression can also induce steatosis. Oxidative stress[29] and gut flora/cytokines[30] can induce steatosis as well as necroinflammation and fibrosis. Free fatty acids (FFA) can initiate hepatocyte apoptosis[31] in addition to being esterified to triacylglycerol. Endoplasmic stress can also lead to steatosis, oxidative stress and apoptosis[32]. Steatosis should therefore be considered part of the liver's early 'adaptive' response to stress, rather than a first hit in disease progression.

Diagnosis:

Symptoms

As with many other types of chronic liver disease, most patients with NAFLD (48–100%) [33-35] are asymptomatic. The liver disease is often discovered incidentally during routine laboratory examination when a hepatic panel reveals an elevated ALT level [36]. NAFLD is the most common cause for unexplained persistent elevation of ALT levels once hepatitis C and other chronic liver diseases have been excluded [37].When symptoms occurs they are usually nonspecific. Vague right upper quadrant abdominal pain, fatigue, and malaise are the most common of these nondescript symptoms [38]. Rarely, pruritus, anorexia, and nausea may develop. Jaundice, abdominal distension (ascites), gastrointestinal bleeding, and confusion

(encephalopathy) are all indicative of advanced liver disease (decompensated cirrhosis), occurring late in the course [39].

Signs

There are no pathognomonic signs of NAFLD. Obesity is the most common abnormality on physical examination, occurring in 30–100% of patients in various cross sectional studies [33,35,36]. Hepatomegaly has been reported in up to 75% of patients in several studies [34,36].The prevalence of hepatomegaly may increase to 95%when assessed by ultrasonography. Stigmata of portal hypertension appear to occur less frequently, although splenomegaly was noted at the time of diagnosis in 25% of patients in one study [36]. Of the various stigmata, spider nevi and palmer erythema are the most common [34]. Muscle wasting may occur as liver disease becomes more advanced but is often underestimated due to edema and preexisting obesity[39].

Laboratory findings:

Mild to moderate elevation of serum aminotransferases (ALT and AST) is the most common and often the only laboratory abnormality found in patients with NAFLD [40].There is no significant correlation between the degree of serum aminotransferases elevation and the histologic severity

of hepatic inflammation or fibrosis [34,41,42]. Unlike those with alcohol-induced steatohepatitis, who typically manifest disproportionate increases in the AST level relative to the ALT level, patients with NAFLD usually have an AST/ALT ratio <1 [34,35,36]. The AST/ALT ratio tends to increase with the development of cirrhosis, thus losing its diagnostic accuracy [40]. Serum alkaline phosphatase[33, 43] may also be slightly elevated in about one-third of patients. Hyperbilirubinemia, hypoalbuminemia, and prolongation of the prothrombin time are noted infrequently and generally only seen once liver failure has become established. Elevated serum lipid profiles and glucose

concentrations are also common in NAFLD patients, reported in 25 to 75% of cases [44].

A small percentage of patients with NAFLD may have a low-titer (<1: 320) antinuclear antibody (ANA) positivity [36,45]. The role of iron in the pathogenesis of NAFLD remains controversial. Bacon *et al*. first reported

that many patients with NASH had biochemical evidence of iron overload .[33]

Several series have shown an elevation of transferrin saturation (in 6–11%) and serum ferritin level (in approximately 50%), however, the hepatic iron

index is consistently <1.9 [33,40]. The significance of HFE mutations in NASH remains to be fully established.

It is important to exclude secondary causes of hepatic fat so that the diagnosis of primary NAFLD can be made reliably. Hepatitis C (HCV) [34] and alcoholic liver disease are particularly important because of the high prevalence of these two hepatotoxic agents. HCV can cause histologic

changes that closely resemble NAFLD[46], thus serologic testing such as HBsAg, Anti HCV to exclude viral hepatitis has become a prerequisite for the diagnosis of NAFLD. By its very definition, the diagnosis of NAFLD cannot be made in the setting of excessive alcohol consumption. Hyperlipidemia may be present. Increased triglycerides are common in children and in patients with metabolic syndrome. Fasting insulin and glucose level will alert the clinician to potential glucose intolerance.

Imaging:

Several noninvasive imaging techniques, including ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI), can identify hepatic steatosis and have been advocated as diagnostic tests for NAFLD. Of these, US are the least expensive. The

sonographic findings of diffuse fatty change include a diffuse hyperechoic echotexture (bright liver), increased liver echotexture compared with the kidneys, vascular blurring,

and deep attenuation[47]. Fatty infiltration of the liver produces a low-density hepatic parenchyma on CT scanning[48]. In a direct comparison of CT with US, US was found to be more sensitive in detecting fatty change[49]. However, when fatty change is patchy or focal, CT scan and MRI are superior to US [50]. Also, when a semiquantitative assessment is required or when multiple comparative studies are planned over time, CT is superior to US [39].

Magnetic resonance spectroscopy is a newer innovative radiologic technique allowing one to examine the resonance frequencies of all proton species within a region of interest and is being investigated as a means of obtaining

a more quantitative assessment of fatty liver infiltration[51]. Despite the utility of these imaging modalities in the diagnosis of diffuse fatty disorders of the liver, none is sufficiently sensitive to detect hepatic inflammation, fibrosis, or cirrhosis. With the inability to distinguish simple steatosis from steatohepatitis and stage the severity of injury, liver biopsy remains the best diagnostic test for steatohepatitis (NASH).

Liver biopsy:

The major histologic features of NAFLD resemble those of alcohol-induced liver disease and include steatosis (fatty liver), steatohepatitis (fatty liver plus parenchymal inflammation with or without accompanying focal necrosis), and varying degrees of fibrosis, including cirrhosis. Steatosis is predominantly macrovesicular and usually is distributed diffusely throughout the liver lobule, although prominent microvesicular steatosis and zone 3 (perivenular) steatosis have been reported occasionally. Mild lymphocytic, neutrophilic, or mixed inflammatory infiltrates also may be observed, and glycogenated nuclei are common.

NASH, which is an advanced form of NAFLD, is indistinguishable histologically from alcoholic hepatitis. Steatosis is present in all cases and can affect the hepatic lobules either diffusely or primarily in the central zones. The degree of steatosis may correlate with the patient's BMI and generally is more severe in NASH than in alcoholic hepatitis.[52] Lobular inflammation is a hallmark feature of NASH and is characterized by infiltration of lymphocytes, other mononuclear cells, and polymorphonuclear neutrophils. Glycogenated nuclei may be present. Hepatocyte ballooning and hepatocyte necrosis of varying degrees often are present and may portend a worse prognosis.[53,54] Mallory (or Mallory-Denk) bodies, which may be small, sparse, and inconspicuous, are seen frequently. Mild stainable iron may be present in up to 50% of the patients. Pericellular, perisinusoidal, and periportal fibrosis has been described in 37% to 84% of patients with NASH. The extent of fibrosis varies considerably, ranging from delicate strands surrounding small veins or groups of cells to densely fibrotic septa with distortion of the hepatic architecture. Perisinusoidal fibrosis is most common, especially in adults, is initially mild, and predominates in zone 3 around the terminal hepatic veins. [55] Cirrhosis is found on initial biopsy in 7% to 16% of patients with NAFLD and abnormal liver biochemical test levels.[56,57] The risk of cirrhosis in the setting of NAFLD may be greatest in morbidly obese patients. In NAFLD-associated cirrhosis, the typical histologic features of NAFLD may be minimal or absent, potentially leading to the misdiagnosis of cryptogenic cirrhosis.

Noninvasive Markers of Fibrosis in NAFLD

Although percutaneous liver biopsy remains the standard for the diagnosis of NAFLD, it is costly, invasive, and associated with a small risk of complications. Sampling variability is common, and the large number of persons with NAFLD far outstrips the manpower available to perform liver biopsies. Significant progress has been made in developing simple, noninvasive, and quantitative tests to estimate the degree of hepatic fibrosis in a number of liver diseases, including NAFLD. The Fibro Test (called Fibro Sure in the United States) is the best studied of these noninvasive tests. The panel of blood tests used to estimate hepatic fibrosis includes serum $á_2$-macroglobulin, apolipoprotein A-1, haptoglobin, total bilirubin, and GGTP levels, and the necroinflammatory activity index combines the same five markers plus the serum ALT level. In a study of 167 patients with NAFLD, Fibro Test was highly sensitive for detecting bridging fibrosis and cirrhosis.[58] Fibro Test cutoff value of .70 had a positive predictive value of 73% and a specificity of 98% for advanced fibrosis. A cutoff value of 0.30 had a negative predictive value of 90% for

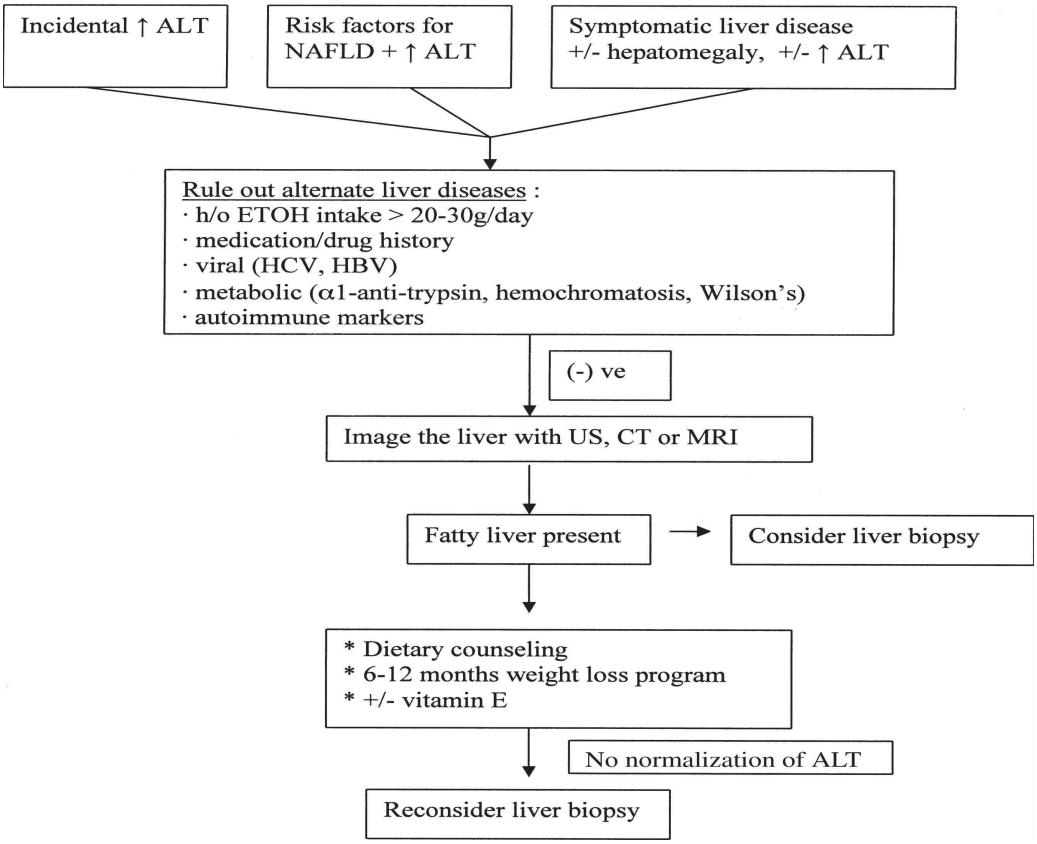

Fig.-1: *Diagnostic approach to NAFLD*

advanced fibrosis. Unfortunately, 33% of patients had a FibroTest score between 0.30 and 0.70, and in this range, the test is inaccurate for assessing the stage of fibrosis. Therefore, patients with a score in this range would need a liver biopsy for accurate staging.

Angulo and colleagues developed and validated another noninvasive fibrosis scoring system called the NAFLD Fibrosis Score, which is derived from clinical and laboratory information that is obtained easily in the context of any clinical encounter. [59] Using this scoring algorithm, which incorporates age, BMI, hyperglycemia, AST/ALT ratio, platelet count, and serum albumin level, the authors defined a low cutoff value with a negative predictive value of 88% to 93% and a high cutoff value with a positive predictive value of 82% to 90%. Only 25% to 28% of cases were indeterminate and would therefore require liver biopsy for accurate staging. Additional noninvasive tests for fibrosis have been evaluated with variable success in small studies of NAFLD, including transient elastography (Fibroscan), which uses ultrasound to quantify liver stiffness and estimate fibrosis, [60] serum dehydroepiandrosterone levels, [61] and serum hyaluronic acid levels. [62] One or more noninvasive indices of fibrosis is likely to be validated in the future and may supplant the need for liver biopsy in many, but not all, patients with NAFLD.

Treatment:

The optimal therapy for NAFLD has not been established. To date, no large, randomized treatment trials demonstrating resolution of steatosis, inflammation, and fibrosis have been conducted in patients with NAFLD. Historically, the treatment of NAFLD has consisted of weight loss, removal of offending drugs and toxins, and control of associated metabolic disorders, including diabetes mellitus and hyperlipidemia. Several case reports and small studies of diet and exercise have shown improvements in biochemical, ultrasonographic, and in some cases, histologic abnormalities in children and adults with NASH. [63-65] Several small, largely uncontrolled studies

also showed improvements in liver biochemical test results, steatosis, and fibrosis in a few patients who achieved modest weight loss with orlistat, a reversible inhibitor of gastric and pancreatic lipases.[66]

A recommendation for moderate weight loss is reasonable in overweight patients with NAFLD, although sustained weight loss is seldom achieved. Rapid weight loss can exacerbate steatohepatitis in morbidly obese patients, especially after bariatric surgery [67]; therefore, the rate of weight loss and serial liver biochemical test results should be monitored carefully in patients on a weight reduction regimen. New therapeutic methods should capitalize on today's improved understanding of the pathogenesis of NAFLD.

Table-II

Potential Therapies for Nonalcoholic Fatty Liver Disease

Avoidance of toxins
Discontinue potentially offending medications/toxins
Minimize alcohol intake
Exercise and diet
Moderate, sustained exercise and weight loss in overweight patients
Effects of specific diets are not known
Antidiabetic/insulin-sensitizing agents
Metformin
Thiazolidinediones
Lipid-lowering agents
Gemfibrozil
Statins
Antioxidants
Betaine
N-acetylcysteine
Superoxide dismutase
Vitamin E
Iron reduction by phlebotomy
Inflammatory mediators by:
Agents that affect increasing mitochondrial ATP stores and/or activity
Agents that affect modulating leptin activity
Agents that affect modulating TNF-α activity
Agents that affect raising adiponectin levels
Bariatric surgery for morbid obesity

ATP, adenosine triphosphate; TNF-α, tumor necrosis factor-α.

Antioxidants:

Medications that minimize oxidative stress may prove useful. Vitamin E, an inexpensive yet potent antioxidant, has been examined as an agent for treatment of NAFLD in several small pediatric and adult studies, with varying results. [66,68-70] In all studies, vitamin E was well tolerated, and most studies showed modest improvements in serum aminotransferase levels, ultrasonographic appearance of the liver, and, infrequently, histologic findings. Randomized controlled studies with histologic inclusion criteria and end points are needed, however, to determine if vitamin E, either alone or in combination with other medications, leads to histologic improvement in NAFLD.

Betaine, a metabolite of choline that raises SAM levels and decreases cellular oxidative damage, has shown promise in a small pilot study as a therapeutic agent for NASH. [71] *N*-acetylcysteine, superoxide dismutase, and PPAR-á agonists such as ragaglitazar also may hold therapeutic promise, [72-74] although clinical studies in humans are lacking.

Insulin-Sensitizing Agents

The association between hyperinsulinemic insulin resistance and NAFLD provides a logical target for treatment. Metformin, a biguanide that reduces hyperinsulinemia and improves hepatic insulin sensitivity, reduces hepatomegaly and hepatic steatosis in ob/ob mice, [75] but results in human studies have been less impressive.[76, 77] Thiazolidinediones (TZDs), potent PPAR-α agonists, also are being investigated as possible agents for the treatment of NAFLD. PPAR-á is a nuclear receptor expressed in adipose tissue, muscle, and liver. In adipocytes, PPAR-α promotes cell differentiation and decreases lipolysis and FFA release. TZDs improve insulin sensitivity and hyperinsulinemia by increasing glucose disposal in muscle and decreasing hepatic glucose output. Rosiglitazone and pioglitazone, TZDs with low rates of hepatotoxicity, have been investigated in separate 48-week, single-arm treatment trials in patients with histologically proven NASH. [78,79] In both studies, treatment was well tolerated and was associated with improved insulin sensitivity, normalization of liver biochemistries, and histologic improvement in most patients. A drawback of both TZDs, however, was substantial weight gain (4.0% to 7.3%) and increased total body adiposity.

Iron Reduction

High serum iron and ferritin levels have been identified in some patients with NAFLD, most of whom do not have genetic hemochromatosis or hepatic iron overload. Most investigators believe that increased serum iron indices are a by-product of hepatic inflammation, rather than a contributor to the pathogenesis of NAFLD.

Lipid lowering agents:

The usefulness of lipid-lowering and cytoprotective drugs for the treatment of NAFLD has been assessed in a few small trials, with varying results. Treatment with gemfibrozil was associated with biochemical improvement in 74% of patients in the treatment group, compared with 30% of untreated control subjects, but histologic features were not assessed. [80] Treatment of NASH with atorvastatin, a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor, showed promise in a small pilot study, [81] but statins have not been assessed in a large clinical trial levels**.**

Cytoprotective Agents:

Ursodeoxycholic acid, a cytoprotective agent, showed promise in a pilot study of NASH but was not effective in a randomized placebo-controlled trial.[82] The combination of ursodeoxycholic acid and vitamin E has shown some efficacy. Future therapies for NAFLD might include agents that increase adiponectin levels, neutralize TNF-α, improve mitochondrial ATP homeostasis, or alter leptin.

Bariatric surgery:

Bariatric surgery leads to massive weight loss and improves insulin sensitivity in most patients, normalizes some of the metabolic abnormalities involved in the pathogenesis of NAFLD, decreases the hepatic expression of mediators of liver inflammation and fibrosis, and improves hepatic histology in patients with NAFLD.[83-87]

Hepatoprotective agents such as pentoxyfilline[88] or probucol were not convincingly effective in randomized trials. Only preliminary uncontrolled trial results are available for omega-3 polyunsaturated fatty acids and sartans. Given the current data and what has been discussed, a recommendation for pharmacologic therapy of NASH could be either a 1-2 year course of therapy with glitazones or vitamin E, preferably in association with high dose ursodeoxycholic acid.

Liver Transplantation

Patients with NAFLD in whom end-stage liver disease develops should be evaluated for liver transplantation. The outcome of liver transplantation in these patients is good, although NAFLD can recur after liver transplantation.[89] The risk factors for recurrent or de novo NAFLD after liver transplantation probably are multifactorial and include hypertriglyceridemia, obesity, diabetes mellitus, and glucocorticoid therapy.

Summary

NAFLD is an increasingly important chronic liver disease with a wide spectrum of histopathology, ranging from bland steatosis to cirrhosis. Insulin resistance and oxidative stress play critical roles in pathogenesis. NAFLD

is often asymptomatic and discovered incidentally on routine laboratory screening. It may occur in isolation or in association with other liver diseases, such as HCV. Liver biopsy remains the most sensitive and specific means of providing prognostic information. In the absence of established

therapies, treatment is generally directed at optimizing body weight and controlling risk factors. Metformin, pioglitazone, vitamin-E and ursodeoxycholic acid have some role in treatment of NAFLD patient. Liver transplantation is a therapeutic option for decompensated liver disease but NAFLD has the potential to recur in the allograft. Large, long-term, biopsy-controlled prospective studies will provide much-needed information about the natural history, treatment, and prognosis of this poorly understood disorder.

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