Nonalcoholic Fatty Liver Disease from the Perspective of an Internist

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Nonalcoholic fatty liver disease (NAFLD) is increasingly recognized as one of the most common causes of chronic hepatitis. While it has an indolent course in most patients, progression to cirrhosis is seen in some. Epidemiological data suggest that NAFLD may be the underlying disease in some patients with so called cryptogenic cirrhosis. Its incidence is likely to increase along with the current epidemiological trends in obesity. An increasing number of observations link insulin resistance as the central mechanism for hepatic steatosis. The factors that determine the progression of the disease, however, remain unclear. A clinical diagnosis is possible in most patients and liver biopsy is seldom required. While weight loss remains the most effective treatment, trials with insulin sensitizing agents are underway. There are some animal data as well as preliminary human data showing that metformin might offer some benefit in NAFLD. Liver transplantation is the treatment of choice for patients with decompensated cirrhosis.

Nair S. Nonalcoholic fatty liver disease from the perspective of an internist. The Ochsner Journal 2002; 4:92-97.

The term nonalcoholic steatohepatitis (NASH) was originally used by Ludwig et al (1980) to describe liver biopsy findings resembling alcoholic hepatitis in patients who did not consume alcohol (1). Later, the term nonalcoholic fatty liver disease (NAFLD) was used to describe a host of pathological findings resulting from the accumulation of fat in the liver. It includes steatosis (fat accumulation without inflammation) along with steatohepatitis and steatonecrosis (inflammation and necrosis in addition to fatty infiltration) and cirrhosis. This review focuses on the clinical aspects of the disease and provides a rational approach to evaluation and treatment of this condition.

Pathogenesis

A brief overview of pathogenesis is relevant for a better understanding of the clinical aspects of the disease as well as the treatment options. NAFLD is a two-stage disease. The initial process is fat (triglyceride) sequestration in the hepatocytes (2,3), which can be caused by multiple factors (Figure 1). Triglyceride can accumulate in liver cells due to an increased influx of fatty acid precursors, diminished beta oxidation of fatty acids (due to congenital or acquired defects in oxidation enzymes, alterations in proteins that transport fatty acids into the mitochondria, or drug toxicities affecting mitochondria), and deficient packaging and export out of the liver cells. However, most authorities now feel that insulin resistance is central to the pathogenesis of this disorder. Release of fatty acids by adipocytes that are insensitive to insulin explains the association of NAFLD with syndrome X, which is typified by diabetes, hypertension, and obesity.

The second stage in the pathogenesis of NAFLD is characterized by inflammation and necrosis of fat-laden hepatocytes. It is not clear what triggers this second insult. Lipid peroxidation is believed to play a crucial role in initiating and perpetuating the inflammation. Increased expression of microsomal CYP2E1 enzymes have been described in both animals and humans with fatty liver (4,5). It is also possible that in some individuals there could be an increased susceptibility to endotoxin, increased exposure to gut-derived toxins and alcohol, or defects in the mitochondria's ability to handle the oxidative stress (5-8). Chronic inflammation may ultimately progress to cirrhosis in some patients (9) (Figure 2).

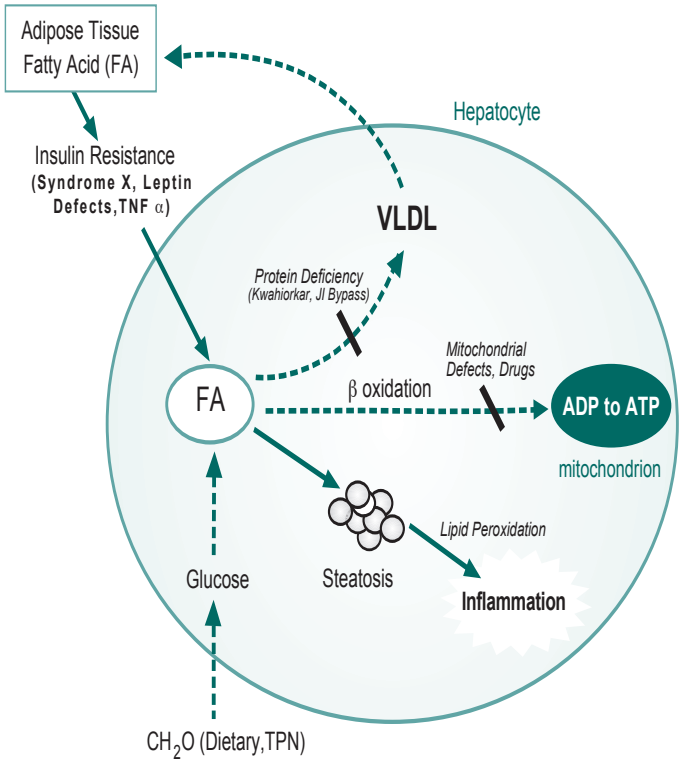

Figure 1. The pathogenesis of steatosis. Dotted line represents the normal pathways of fat transport and metabolism in the liver. The solid arrows represent the likely source of steatosis.

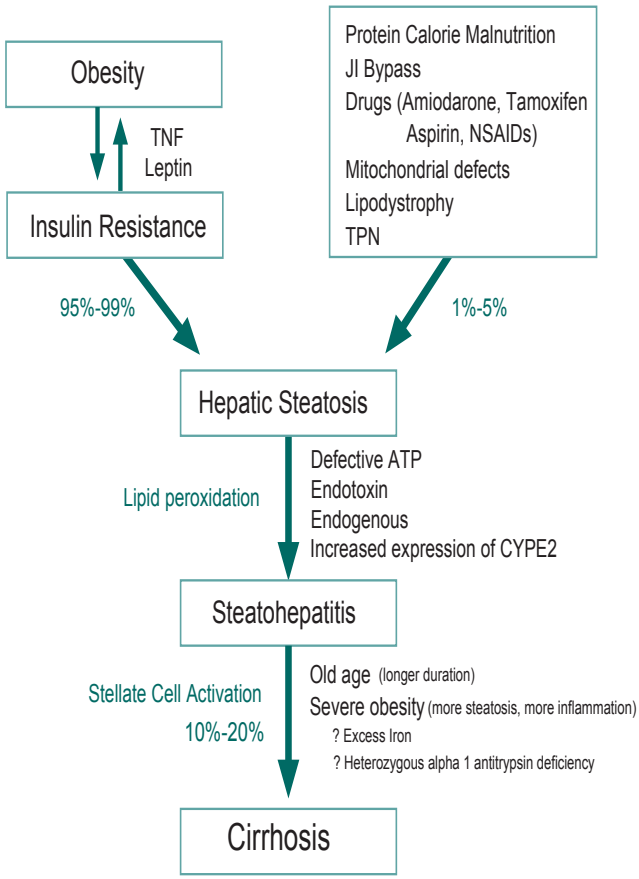

Figure 2. The etiology and natural history of NAFLD.

Prevalence

Even though no large studies based on liver biopsy have been done, a recent analysis of the third National Health and Nutrition Survey (NHANES) showed that at least 30% of adults in the United States have abnormal transaminases, which is roughly the same percentage of Americans who are obese (10). Since viral and autoimmune serologies were negative in these cases, the majority of patients were presumed to have NAFLD. In the NHANES study, a cut off of 30 IU/L was used as the upper limit of normal for aspartate serine transaminase (AST), and hence the incidence may have been slightly overestimated. In a large autopsy series of 351 nonalcoholic subjects, histological changes similar to NASH were found in 6.3% (11). From these studies one could infer that NAFLD is an extremely common condition and likely to be far more common than hepatitis C. The prevalence is likely to be much higher in obese patients. In a European study, at least 70% of obese patients had ultrasonographic evidence of fatty liver (12).

When to Suspect NAFLD

NAFLD is the most likely cause of elevated transminases in patients who have features of insulin resistance syndrome. Patients are usually middle aged and have a history of recent weight gain, diabetes, hypertriglyceridema, or hypertension. Many patients, especially those with significant hepatomegaly, may complain of right upper quadrant discomfort, but severe pain is uncommon. Massive hepatomegaly is seen in some patients, especially in those who have had severe weight gain over a short period of time. The serum transaminase levels are typically in the ranges of 1.5-3 times the normal limit with levels above 300 IU/L being unusual. Alanine transaminase (ALT) is usually elevated more than AST, and in most patients AST is often normal with only a mildly abnormal ALT. This is unlike alcoholic hepatitis where AST is usually higher than ALT. As has been reported with chronic viral hepatitis, AST tends to predominate should the disease progress to advanced fibrosis and cirrhosis. The increase in transaminases need not always reflect

steatonecrosis or steatohepatitis as many patients with steatosis alone can have elevated ALT or AST. Alkaline phosphatase (ALP) is usually normal in NAFLD. A markedly increased ALP (i.e. > 3 times normal) is a not a feature of NAFLD and warrants further evaluation by ultrasound and liver biopsy or cholangiography.

Proceeding With a Typical Evaluation

In a typical patient with features of insulin resistance (obesity, diabetes, hyperlipidemia, and hypertension), mild transaminase elevation is most likely due to NAFLD. It is always prudent to exclude other treatable liver diseases such as hepatitis C (especially if risk factors are present), autoimmune hepatitis, and hemochromatosis. A positive antinuclear antibody test (ANA, usually in low titers) is seen in many patients with NAFLD (10%-20%). A proper history of alcohol intake is very important and, apart from a good history, there are no reliable serological or imaging studies to distinguish alcoholic fatty liver from NAFLD.

Imaging studies

All imaging modalities appear to have comparable sensitivity, and ultrasound is probably the safest and least expensive. Nuclear imaging studies such as xenon scintigraphy may also show uptake of fat in the liver but have not been shown to be more specific than other imaging studies such as liver ultrasound. None of the imaging studies are indispensable tools to diagnosis, and the clinician should suspect the diagnosis whenever an obese patient presents with hepatomegaly, abnormal serum aminotransferase tests, and no other obvious cause for elevated transaminase levels.

Liver biopsy

Histology is the only way to distinguish steatosis from steatohepatitis (or steatonecrosis) as serum transaminase values can be elevated in both. Similarly, there are no serological tests to determine the degree of fibrosis. However, a clinical diagnosis is possible in almost all patients, and liver biopsy is seldom required for diagnosis alone.

The only role for a liver biopsy in NAFLD, outside the setting of a clinical trial, is to provide information with respect to the stage of disease (i.e., the amount of fibrosis). An enlarged spleen and thrombocytopenia may suggest advanced fibrosis or cirrhosis, and such patients may need a biopsy for accurate assessment of their liver disease.

How Serious Is NAFLD?

NAFLD can lead to progressive liver damage and cirrhosis. It is not exactly known what percentage of patients progresses to cirrhosis. It has been variously stated that 20% of patients may develop cirrhosis, although a controlled longitudinal study with serial biopsies is not available. Two recent case controlled studies suggested that NAFLD may be the underlying liver disease in a large number of patients with so-called "cryptogenic cirrhosis" (13,14). Since cryptogenic cirrhosis typically accounts for 5%-10% of adult patients undergoing liver transplantation, it is reasonable to assume that NAFLD may be the underlying liver disease in at least 5% of transplanted patients (15). In addition, NAFLD is underrepresented in transplant databases as it is usually acquired in the fourth or fifth decade and by the time cirrhosis develops patients may not be appropriate candidates for transplantation. The relatively late onset of NAFLD has important implications in the geriatric population, however, where it may be one of the most common causes of newly diagnosed cirrhosis. Importantly, because fat deposition is often reduced as the disease advances, the lack of steatosis in a cirrhotic liver should not dissuade the clinician from assuming that NAFLD is not the etiology of cryptogenic liver disease.

In a retrospective review from Cleveland Clinic that assessed the long-term mortality among patients with biopsy-proven NAFLD, liver failure was the second most common cause of death (cardiac events were the first) (16). This suggests that NAFLD has important prognostic implications and should not be considered a benign condition.

There are no long-term studies that have defined the rate of progression of NAFLD. It is likely a slowly progressive disease that develops into cirrhosis during 20 or more years. Several studies have shown that advanced age is a risk factor for fibrosis (17). The risk of hepatocellular carcinoma (HCC) is not well defined in NAFLD. A study based on incidental HCC in patients with cryptogenic cirrhosis, suggests that primary liver cancer is likely to occur less frequently in patients with NAFLD than viral hepatitis but more commonly than primary biliary cirrhosis or autoimmune liver disease (18).

Commonly Used Drugs and NAFLD

Statins

Use of antihyperlipidemic agents in NAFLD deserves special mention. Since hyperlipidemia is seen in many patients with NAFLD, the critical question is whether it is safe to use these potentially hepatotoxic medications in this disease. Unfortunately, there are no studies regarding the safety of these agents in NAFLD. One reasonable approach, which we often use in practice, is to assess the histological severity of NAFLD and, if the disease is mild, we often proceed with a statin. Liver function tests are monitored every 3 months and medication is discontinued should an abrupt increase in transaminase activity be seen. While solid evidence for benefit is lacking, hyperlipidemia is an extremely common problem in these patients, and sometimes control of hyperlipidemia might itself decrease steatosis. In addition, mortality related to

cardiovascular events is more common in these patients (16) and, hence, minimizing its risk is probably as important as treating the liver disease.

Hormonal Treatments

Oral contraceptives have been associated with cholestatic liver disease. Tamoxifen, a partial estrogen agonist that has been commonly used as an adjuvant in patients with breast cancer, is well known to cause steatosis and steatohepatitis (19). However, there are no reports of steatohepatitis caused by estrogens. It is also highly unlikely they will influence the course of steatohepatitis. Since patients with NAFLD are often middle-aged obese women, they are at high risk for osteoporosis, and it is probably not wise to withhold estrogen replacement treatments in these patients.

NSAIDS

Nonsteroidal anti-inflammatory agents (NSAIDS) have been known to cause mitochondrial dysfunction, and a fatal case of microvesicular steatosis has been reported with ibuprofen. However, reports of NSAIDS causing NAFLD in a consistent manner are lacking, and there is no reason to withhold treatment with these agents in patients with NAFLD.

Treating NAFLD

As explained previously, NAFLD is a two-stage disease, the first being excess accumulation of triglycerides in the hepatocytes. Since insulin resistance and obesity play a central role in NAFLD, weight loss is the mainstay of treatment. Gradual weight loss can lead to mobilization of hepatic fat via enhanced beta-oxidation as more fat is used for caloric needs. The weight loss program should be centered on the caloric restriction rather than alteration of dietary contents. Even though the human body initially uses carbohydrates for energy needs, a sustained deficiency in calories necessitates utilization of stored triglycerides in the liver and ultimately the adipose tissue. Since hepatic triglycerides are used more efficiently in early stages of caloric deficiency, minimal weight loss may be sufficient to see an improvement in serum transaminase levels. This is extremely common in clinical practice as a weight loss of 5-10 pounds often results in normalization of transaminases. Rapid weight loss by severe caloric restriction is harmful, however, as it exaggerates fat mobilization from peripheral adipocytes, in turn aggravating the steatosis. Such effects have been seen in morbidly obese patients undergoing intestinal bypass or gastric stapling procedures. Alteration in the content of the diet without restricting calories may sound attractive. One such example is the 'sugar buster' diet. In this type of diet, severe restriction of carbohydrates depletes hepatic glycogen stores forcing utilization of accumulated fat in the liver and adipose tissue. Although some patients who are on this diet have lost weight and normalized their transaminases, the safety and efficacy of diets involving severe restrictions of carbohydrates need further evaluation before this can be accepted as therapy for NAFLD. Besides, it is often difficult to follow these diets over prolonged periods. Since NAFLD is a slowly progressing disease, only a sustained reduction in steatosis might influence the natural history. Often patients want to restrict fat in the diet, and fat restriction alone without restricting calories is futile as excess carbohydrates can easily be converted into fat. As shown in the long-term follow up study from the Cleveland Clinic (16), the most common cause of death in these patients is cardiac events and the overall benefit of weight reduction on other manifestations of syndrome X may be equally important in treating these patients.

Drugs

Because of the complexity of the pathophysiology of NAFLD, drug treatment is often difficult. Few studies in the past have attempted treating NAFLD using ursodeoxycholic acid (Actigall, Novartis Pharmaceuticals, East Hanover, NJ; Urso, Axcan Scandipharm Inc., Birmingham, AL), vitamin E, insulin sensitizing agents and betaine. Among these, insulin sensitizing agents appear to be the most promising as they address the primary problem in these patients.

Insulin Sensitizing Agents

Metformin: The most convincing data on the benefit of metformin comes from studies of ob/ob mice (leptin-deficient mice with features of insulin resistance and marked hepatic steatosis). Ob/ob mice treated with metformin had substantial weight loss with disappearance of hepatic steatosis compared with pair fed mice (20). The histological improvement after treatment was remarkable. In addition, metformin also decreased TNF alpha expression (improves sensitivity to insulin), decreased uncoupling protein (UCP-2) expression (leading to improved ATP generation by hepatocytes), and down-regulated sterol-binding receptors (decreases fatty acid synthase). Two other studies, including one from our own group, have evaluated the efficacy of metformin in human NAFLD. In a recently published European study, a 3-month treatment with metformin resulted in improvement in AST and ALT compared with a group of patients treated with diet alone (21). In our open labeled study in which treatment is given for 1 year, we have had encouraging initial results with major improvements in AST and ALT occurring in roughly one third of patients. However, the histological data are awaited, and this will be critical to any conclusions. The experience and the data from Europe show that lactic acid accumulation is not a major problem in these patients.

However, whether the safety can be extrapolated to long-term treatment is not clear. It is also pertinent that the dramatic results in the mouse model were obtained by using doses as high as 50 mg/kg body weight, whereas the maximum allowed dose in humans is 20 mg/kg. In animal studies, metformin caused substantial weight loss and it is not clear whether the weight loss was primarily responsible for the beneficial effects of metformin. The initial observations from our study also point to this.

Troglitazone: A pilot study using troglitazone in the treatment of NASH showed modest benefit (22); however, this drug was withdrawn due to serious hepatotoxicity.

Betaine: A naturally occurring metabolite of choline, betaine has been shown to raise S-adenosylmethionine (SAM) levels and improve fatty acid metabolism. A small pilot study in 10 patients showed some improvement in transaminases (23) and it was relatively well tolerated.

Ursodeoxycholic acid: Ursodeoxycholic acid is a synthetic bile acid generally used in cholestatic liver diseases. It is believed to have some membrane stabilizing action on the hepatocytes and has been used in treating patients with NASH (24). Its benefit, however, appears to be limited.

Vitamin E: Since inflammation and necrosis in NAFLD are believed to be the result of lipid peroxidation and free radical injury in fat-laden hepatocytes, a free radical scavenger such as vitamin E has been used in treating NASH. Even though some studies have suggested improvement in the biochemical profile, a controlled study evaluating liver histology is not available (25,26). The benefit of vitamin E is likely to be modest in NAFLD. However, considering its excellent safety, small doses of vitamin E may be used in these patients.

Liver Transplantation

Patients who have progressed to cirrhosis should be considered for transplant if they have evidence of decompensation. As mentioned earlier, NAFLD may account for only 5% of adult cases coming to liver transplantation. This is a small number considering the disease prevalence. This again underscores the relatively late onset and slow progression of the disease. Provided the comorbid illnesses such as cardiac status are stable, these patients generally do well after transplant. Fatty liver almost always recurs in the new liver (27) since these patients tend to gain more weight after transplant and their primary defect, insulin resistance, is not corrected by transplant. However, it is unlikely that recurrent disease would cause graft loss.

Conclusion

NAFLD is a relatively common disorder associated with obesity and insulin resistance. There is a small but definite risk of progression to cirrhosis over a few decades. Recent epidemiological studies indicate that NAFLD might be the underlying disease in the majority of patients with "cryptogenic cirrhosis." The mainstay of treatment is weight loss, as pharmacological treatment has not been very successful. However, drugs that improve insulin resistance hold promise especially in decreasing steatosis. Further studies are required to determine whether these drugs will prevent progression to cirrhosis.

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