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Non-alcoholic fatty liver disease and metabolic syndrome: what we know and what we don't know

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Summary

NAFLD is a very common asymptomatic liver condition that may progress to cirrhosis and hepatocellular carcinoma, and a relation to the different components of the metabolic syndrome has been found. In this review we highlight some of the epidemiological aspects of the two disorders and discuss some of the possible mechanisms and questions to be answered concerning the risk factors for the progression of this condition as well as the need for more studies to focus on possible modalities of treatment.

key words: non-alcoholic fatty liver • diabetes • insulin resistance

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EPIDEMIOLOGY

Diabetes mellitus (DM) is a common endocrine problem. It is rapidly becoming a major health problem worldwide [1]. A study conducted by Mokdad et al. [2] detected a 33% increase in the prevalence of diabetes in adults across all age-groups, races, education levels, weight levels, and levels of smoking over an 8-year period (1990–1998). Non-alcoholic fatty liver disease (NAFLD) was first described by Ludwig and his colleagues at the Mayo Clinic in 1980 as a liver condition that pathologically resembles that of alcohol-induced liver injury but it occurs in patients who do not abuse alcohol [3]. It is an increasingly recognized condition that may progress to end-stage liver disease and hepatocellular carcinoma. Several terms have been used to describe this condition, including fatty-liver hepatitis, non-alcoholic Laennee's disease, diabetes hepatitis, non-alcoholic liver disease, and non-alcoholic steatohepatitis. NAFLD is becoming the preferred term [4].

An NAFLD prevalence of 10–24% has been reported in the general population [5–8]. This prevalence increases to 50–55% in type-2 diabetics and patients with hypertriglyceridemia [9–11] and to 75% in obese persons [12], where truncal obesity seems to be an important risk factor even in patients with normal body mass index [13]. The reported prevalence of obesity in several series of patients with NAFLD range between 30–100%, while it is 10–70% in type-2 diabetics and 20–92% in patients with hyperlipidemia [3,5,14–18]. It seems that the most common risk factor associated with NAFLD is the presence of metabolic syndrome, which is defined as the presence of 3 or more of the following criteria: [1] increased waist circumference, [2] hypertriglyceridemia, [3] hypertension, [4] high fasting glucose, and [5] a low high-density lipoprotein (HDL) level [19]. Marchesini and colleagues [20] assessed the prevalence of metabolic syndrome in 304 consecutive NAFLD patients without overt diabetes, this prevalence being 18% in normal weight subjects and increasing to 67% in obese persons. Metabolic syndrome is a common problem [21,22] and, due to the increasing prevalence of metabolic disorders, e.g. obesity, diabetes, hyperlipidemia, and hypertension, a very large population are at risk of developing NAFLD and it will represent a major health concern in the future.

PATHOPHYSIOLOGY

Insulin resistance is the pathophysiological denominator that links all the components of the metabolic syndrome and may have a major role in the development of NAFLD even in lean subjects with normal glucose control [23]. Insulin resistance leads to the accumulation of fat in the hepatocytes by lipolysis and hyperinsulinemia [24,25]. The ob/ob mouse model of obesity and fatty liver has proved very useful in testing hypotheses of pathogenesis that may apply in humans. A study by Li and colleagues [26] found that probiotics (a mixture of viable *Bifidobacterium*, *Lactobacillus*, and *Streptococcus thermophilus*) and antibodies to tumor necrosis factor (anti-TNF) both reduced the degree of fatty infiltration of the liver in ob/ob mice without changing their body weight significantly. These findings suggest that intestinal bacteria may promote hepatic insulin resistance and the development of NAFLD.

DIAGNOSIS OF NAFLD

NAFLD is essentially an asymptomatic condition and the diagnosis is made when a radiological test performed for unrelated indicators reveals evidence of fatty liver or when liver transaminases are elevated. Mild to moderate elevation of ALT or AST or both are the most common findings (with the AST: ALT ratio <1) [27]. However, it has been shown that the degree of ALT elevation does not correlate with liver histology [28]. In patients with NAFLD who do not have advanced liver disease, the most common sign on physical examination is hepatomegaly [3,29]. Sonography is the most commonly used modality for the diagnosis of NAFLD. It has a sensitivity of 89% and a specificity of 93% in detecting steatosis [30]. Although a CT scan is more specific, it is also more expensive. Studies have shown that no radiological modality could differentiate the histological stages of NAFLD; only the severity of steatosis was reflected in these radiological tests. The presence of >33% fat on liver biopsy was optimal for detecting steatosis on radiological images [31]. Liver biopsy remains the gold standard for the assessment of liver histology and a key test to diagnose NAFLD [32], which means that the condition is more common than we think, as most studies on its prevalence depend on radiological testing. There are several histological stages in the progression of NAFLD to cirrhosis. These progressively include: fatty liver alone, steatohepatitis, steatohepatitis with fibrosis, and cirrhosis.

NATURAL HISTORY AND FACTORS AFFECTING PROGNOSIS

The natural history of NAFLD can be temporally divided into three phases. Significant steatohepatitis, necrosis, or fibrosis is very unlikely before a patient reaches age 40. During the 5th decade of life, steatohepatitis may develop and continue to progress. By the age of 60, some patients will have developed cirrhosis that is often interpreted as cryptogenic [33]. It is not possible to predict with accuracy which patients are at risk of progression or development of complications of liver disease, but it seems to be determined by the severity of histological damage. In five series, 54 of 257 patients with NAFLD underwent liver biopsy during an average follow-up of 3.5–11 years; of these, 28% had progressive liver damage, 59% had no change, and 13% had improvement or resolution of liver injury. Patients found to have pure steatosis on liver biopsy seem to have the best prognosis, whereas features for steatohepatitis or more advanced fibrosis are associated with a worse prognosis: cirrhosis and liver-related death occur in 25% and 10% in these patients, respectively, over a 10-year period [5,14,15,34–36]. The natural history of cirrhosis resulting from NAFLD has not been defined. Recent study by Charton et al. [37] found only 2.9% of 546 liver-transplantation procedures performed in a single center were for end-stage steatohepatitis, which means that a minority of patients with NAFLD will require liver transplantation, but the condition may recur after such procedure [38,39] and a second transplant is associated with decreased survival and increased resources utilization [40]. NAFLD-related cirrhosis is associated with a higher likelihood of developing hepatocellular carcinoma compared with cirrhosis with other causes, and the factors for progression are not well characterized [41]. In a study conducted by Marrero and colleagues [42], where 150 consecutive patients with hepatocellular carcinoma were studied, cryptogenic cirrho-

sis was the etiology in 29%, half of them having histological or clinical features associated with NAFLD.

The questions as to what factors determine the progression of NAFLD to cirrhosis, which patients will progress to end-stage liver disease, and which patient will develop hepatocellular carcinoma are not answered yet. Some data suggest that the coexistence of steatosis with other liver disease, such as hepatitis C infection, could increase the risk of progression of liver disease [43]. Would the natural history be affected by the presence of the different components of the metabolic syndrome, i.e. diabetes, obesity, and hyperlipidemia, or will the patient develop NAFLD and it will progress even in the absence of the metabolic components, as he has insulin resistance? In a study conducted by Marchesini and colleagues [20] they noted that the presence of metabolic syndrome carries a high risk of fibrosis and is associated with potentially progressive, severe liver disease. A follow-up study by Powell and colleagues [14] showed that poor glycemic control precedes the onset of steatohepatitis, while another study by Harrison et al. [44] found that BMI was not correlated with progression of NAFLD. Further prospective studies are needed on this important issue.

TREATMENT

There is no specific treatment for NAFLD. Improvement in liver function results and hepatomegaly have been noticed in obese patients with NAFLD after gradual, sustained weight reduction of 10% [45-47], but rapid weight loss may cause progression of NAFLD [45,48]. Treatment of hyperlipidemia may be helpful in the management of NAFLD. Use of clofibrate for 12 months in a series of 16 patients with NAFLD did not result in significant biochemical or histological improvement [49]. However, 23 patients with NAFLD randomized to gemfibrozil in another trial had significant improvement in liver enzymes [50]. The impact of glycemic control on liver histology in patients with diabetes and NAFLD is not known. Diabetic medications that have been shown to correct insulin resistance may prove to be beneficial in treatment. Neuschwander-Tetri and colleagues [51] studied the utility of rosiglitazone in an open-label pilot study and they found that ALT level decreased and hepatic steatohepatitis decreased progressively during therapy. A similar decrease in ALT was noted in another pilot study which used metformin [52]. Harrison et al. [53] studied the effect of an antioxidant consisting of vitamin E and vitamin C on hepatic steatohepatitis in a placebo-controlled trial and they noted less hepatic fibrosis after 6 months. Results of pilot studies evaluating ursodeoxycholic acid, betaine, N-acetylcysteine, and alphatocopherol suggest that these medications may be of potential benefit [54-56]. However, there are no definitive data regarding the use of these drugs in the treatment of NAFLD. Current evidence suggests that the future might be concentrated on agents which improve insulin resistance.

CONCLUSIONS

NAFLD is a very common asymptomatic liver condition that may progress to cirrhosis and hepatocellular carcinoma. A prevalence of 50-55% in type-2 diabetics has been reported. Insulin resistance may have a major role in the development of NAFLD even in lean subjects with normal glucose

control. Sonography is the most commonly used modality for the diagnosis of NAFLD. Liver biopsy remains the gold standard for the assessment of liver histology and a key test to diagnose NAFLD. It is not possible to predict with accuracy which patients are at risk of progression or development of complications of liver disease. Further studies are needed on this issue, as well as more studies to focus on possible modalities of treatment.

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