

NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD) - A NOVEL COMMON ASPECT OF THE METABOLIC SYNDROME

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Non-alcoholic fatty liver disease (NAFLD) is emerging as one of the most common liver disorders claiming the urgent attention of both medical professionals and the public sphere because of the imminent epidemic of advanced liver injury that appendages epidemic of obesity. Recent research reveals simple triglyceride accumulation in hepatocytes (i.e., liver steatosis) frequently becoming complicated by inflammation (i.e., non-alcoholic steatohepatitis, or NASH) that may progress into more advanced stages of the disease including cirrhosis or, eventually, hepatocellular carcinoma. The exact mechanisms of the progression of NAFLD into overt NASH and advanced disease stages are largely unknown. There is urgent need in terms of both intensive research pursuits and effective practical measures to deal with this common threat.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a nosological unit first introduced by Ludwig and his colleagues at the Mayo clinic in 1980¹. It is emerging as the most common liver disorder recognized in Europe and North America. It includes a wide spectrum of hepatic alterations of metabolic origin. According to current estimates, the prevalence of NAFLD in the general population ranges from 5 % to 33 %. Up to more than 75 % of obese adult subjects can be affected by NAFLD²⁻⁴. Formerly a disease of adults, NAFLD now seriously extends to lower-age population segments, the true prevalence remaining unknown. Data obtained by Franzese et al.⁵ have indicated that this condition can be prevalent in as much as 53 % of obese children, and NAFLD is now recognized as an important childhood liver disease, especially since childhood obesity is much more common.⁶⁻⁸ According to estimates, NAFLD is likely to reach epidemic proportions in children worldwide in the next decade^{9,10}.

NAFLD IS A NOVEL COMMON FEATURE OF THE METABOLIC SYNDROME

In most cases, NAFLD is associated with obesity, hyper- or dyslipidemia, and insulin resistance. This close association suggests possible causal links between the disorders. Based on recent research, the condition most

closely associated with NAFLD is obesity and central obesity, in particular¹⁰⁻¹². Widespread hyper- or dyslipidemia supported by inappropriate dietary and lifestyle habits are considered as the most common denominators and key determinants of this undesirable trend^{13,14}. On this basis, NAFLD has been included as part of the metabolic syndrome, or syndrome X¹⁵⁻¹⁷. An available data support this association. A large portion of cases with metabolic syndrome suffer from NAFLD that can be now envisaged as a specific hepatic manifestation of this systemic disorder, both conditions probably sharing common pathogenic mechanism(s)¹⁸⁻²¹. Although representing a special problem among obese people, NAFLD can also occur in non-obese/non-diabetic subjects as well as in patients with lipodystrophy^{3,13,14,22}.

OUTLINE OF THE CLINICAL COURSE

In pure fatty liver, the disease may have a benign clinical course without excess mortality²³. However, contrary to what has been thought previously, fatty liver is not a trivial condition. Simple forms of NAFLD are characterized by triglyceride accumulation in hepatocytes (i.e., liver steatosis). This frequently becomes complicated by inflammation (i.e., non-alcoholic steatohepatitis, or NASH)¹. Unfortunately, the mode and exact rate of progression of NAFLD into more advanced stages of the disease have been characterized only partially. NAFLD may progress

to hepatitis, cirrhosis and, eventually, to hepatocellular carcinoma. Several histological stages have been delineated in the process of progression of NAFLD to cirrhosis. These progressively include: fatty liver alone, steatohepatitis, steatohepatitis with fibrosis, and cirrhosis^{18,24}. According to the recent review, steatosis may develop into NASH in one third of cases², and NASH can be envisaged as a turning point in the development of the disorder^{1,10}. Patients with NASH have a significantly increased risk of cirrhosis. Reportedly, a considerable subset (up to 50 %) of NASH patients can develop fibrosis and about 15 % to 19 % develop cirrhosis. Of note, the 7- to 10-year liver-related mortality due to cirrhosis is 12 % to 25 %. A fraction of NAFLD patients develop hepatocellular carcinoma. The risk in this malignant complication is increased more than 4-times in such patients. About 3 % of cases may progress to terminal liver failure, requiring liver transplantation^{2,10,17,25,26}. At present, up to 4 % to 10 % of liver transplants can probably be accounted for by the liver failure caused by end-stage NASH; this estimate is very likely to rise.² Furthermore, in patients who have undergone liver transplantation, NAFLD frequently recurs^{3,15}.

SYMPTOMS AND DIAGNOSIS

NAFLD is essentially an asymptomatic condition. Non-specific symptoms are present in approximately 30 % of the patients prior to diagnosis. The diagnosis is usually made when liver alanin aminotransferase (ALT) and/or aspartate aminotransferase (AST) enzymes are elevated or when there is a fortuitous ultrasonographic or radiological evidence of fatty liver. Mild to moderate elevation of ALT or AST or both are the most common findings (with the AST:ALT ratio <1) and, according to recent estimates, NAFLD is the most frequent cause of abnormal liver function tests and abnormal liver enzymes on routine blood testing that should be considered as a first presentation of NAFLD or NASH^{1,3,15,27}. However, it has been shown that the degree of ALT elevation does not correlate with liver histology^{24,28}. In patients with NAFLD without manifestation of a more advanced liver disease, the common finding on physical examination may be hepatomegaly^{1,29}. Classification of NAFLD progress into phases 1 to 4 has been proposed based on the morphological biopsy patterns³⁰, and more detailed staging and grading systems have been elaborated.^{18,31} Furthermore, primary and secondary forms of NAFLD have been delineated¹⁰.

No specific laboratory tests or noninvasive investigation to diagnose NASH are available to date. The sensitivity of noninvasive imaging techniques is not adequate since these fail to distinguish NASH from simple steatosis^{10,32,33}. The definite diagnosis of the disease is based on histological criteria. While not every patient with mild elevation of liver enzymes can be referred for a liver biopsy, it is often difficult to make accurate diagnostic decisions^{3,33,34}. Recently, Palekar et al.³⁵ have proposed a diagnostic model aimed at distinguishing patients with simple steatosis from those with NASH. The character-

istics considered by the authors³⁵ are as follows: female gender, age ≥ 50 years, BMI ≥ 30 mg/m², serum AST ≥ 45 IU/l, AST/ALT ratio ≥ 0.8 , and plasma hyaluronic acid concentration ≥ 55 μ g/l. Patients with three or more of these characteristics are more likely to have NASH than simple steatosis³⁵.

PATHOBIOCHEMISTRY AND PATHOPHYSIOLOGY

The liver has been shown to have a high capacity for accumulating triglycerides. For instance, short term fat feeding may lead to an about 3-fold increase in rat liver triglyceride content without increase in visceral or skeletal muscle fat¹⁴. Moreover, the content of intra-abdominal fat has been reported to directly correlate with liver fat¹². According to Thomas et al.³⁶, intrahepatic lipids increase by 22 % for any 1 % increase in total adipose tissue, by 21 % for any 1 % increase in subcutaneous adipose tissue, and by 104 % for 1 % increase in intra-abdominal adipose tissue. Liver fat does not simply reflect fat stores, but is markedly controlled by dietary fat³⁷. Changes in dietary fat can change liver fat independently of any change in body weight, free fatty acid (FA) concentration, intra-abdominal or subcutaneous fat mass, or rate of carbohydrate, lipid or protein oxidation^{12,38}. Up to 20 % of dietary FA are secreted as VLDL triglycerides in humans within 6 hours after a meal^{39,40}. Weight loss enhances insulin sensitivity and subjects with high liver fat submitted to a weight loss showed a larger decrease in hepatic fat and a more marked decrease in insulin concentration than control subjects with low liver fat^{41,42}. Thus, diet may influence steatosis markedly.

Plasma lipid overflow and resulting tissue overload, decreased FA oxidation, increased hepatic synthesis of triglycerides and/or altered secretion of very-low-density lipoproteins (VLDLs) from the liver are probably the most critical contributors to developing NAFLD¹⁰. At the same time, NAFLD is intimately associated with progressive manifestation of insulin resistance in the liver. Importantly, in over-fed animals, insulin resistance in liver and adipose tissue precedes the impairment of insulin sensitivity in skeletal muscle⁴³. Simple (i.e., early) hepatic steatosis alone is insufficient to increase endogenous glucose production in the liver but it is linked to insulin resistance so that higher insulin concentrations are required to control liver metabolism and gluconeogenesis, in particular^{14,44}. Suppression of both direct and indirect (extrahepatic) effect of insulin may be responsible for enhanced liver gluconeogenesis^{45,46}. Transcription factors sterol regulatory element-binding protein-1c (SREBP-1c), peroxisome proliferator activated receptors (PPARs), and carbohydrate response element-binding protein (ChREBP) have been described as the main physiologic molecular regulators of lipogenesis; they are also implicated in the abnormal accumulation of triglycerides in NAFLD. A number of regulatory peptides, particularly those released from adipocytes, such as TNF α , leptin, adiponectin, resistin, visfatin, etc., may be involved in all

phases of liver damage in NAFLD and, subsequently, NASH^{10, 13, 47-51}.

The exact mechanism of the progression of simple steatosis into overt NASH remains unclear. Hepatic lipid accumulation is not the sole factor responsible for hepatocellular injury. Once developed, oxidative stress and diminished antioxidants within the liver can initiate the progression from steatosis alone to NASH and ultimately to cirrhosis^{20, 52}. Increased hepatic FA oxidation can generate reactive oxygen radicals (ROS) that may promote mitochondrial dysfunction, lipid peroxidation, and/or cytokine secretion⁴⁷. A two-hit model has been proposed⁵³ involving a cellular event or events that, in steatotic liver, promote(s) inflammation, fibrosis, cell death, and cirrhosis. Abnormal cytokine secretion, particularly that of inflammatory cytokines (e.g., TNF α , IL-6, etc.), and ROS as well appear as the major players implemented in the conversion of relatively benign steatosis into NASH. Activation of specific redox-sensitive kinases and inflammatory signalling pathways, e.g., inhibitor kappa-B kinase (IKK- β) and nuclear factor- κ B (NF- κ B) cascade, can initiate a self-perpetuating and self-reinforcing positive feedbacks leading to irreversible liver injury that characterizes NASH histopathologically. FA themselves may cause hepatocyte apoptosis, i.e., the final mechanism of cellular injury in NAFLD^{3, 10, 13, 54-56}.

THERAPY AND PREVENTIVE MEASURES

Collectively, the recent research reveals that a large part of human population is susceptible to the serious liver damage brought on by their lifestyle. This fact calls for acceptance of urgent practical measures to tackle the imminent epidemic threat. There is no specific drug treatment available for NAFLD at present. Therefore, treatment strategies lay stress on modifying risk factors of the disease. The importance of calorie restriction, physical activity, and the presence of antioxidants in the diet in NAFLD prevention have been emphasized repeatedly^{9, 20, 37, 47}.

Several pilot clinical studies have convincingly shown that changes in lifestyle may halt NAFLD progression. Ueno et al.⁵⁷ have reported that restricted diet and exercise therapy, such as walking and jogging, are useful means for improving blood biochemical data and histological findings in NAFLD. Investigating NASH patients who successfully completed one year of intense dietary intervention, Huang et al.⁵⁸ have found that these do display histological improvement, thus confirming the effectiveness of dietary intervention in biopsy-proven NASH-affected individuals. Finally, in a group of subjects followed for one year and receiving regular counselling, weight loss and regular exercise have been shown to improve blood ALT levels and increase the clinical odds of normalization of this liver enzyme. Reducing weight by at least 5 % together with subsequent weight control and regular exercising has been revealed as a reasonable target in NAFLD treatment⁵⁹.

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