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NON ALCOHOLIC FATTY LIVER DISEASE: A BRIEF OVERVIEW

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ABSTRACT

The occurrence of non-alcoholic fatty liver disease (NAFLD) is around 20-30% in the general population. NAFLD is usually asymptomatic, although a minority of patients may present with evidence of progressive liver injury with complications of cirrhosis, liver failure, and hepatocellular carcinoma. In spite of being common and potentially serious, relatively little is known about the natural history or prognostic significance of NAFLD. The management focuses upon modifying metabolic risk factors. Insulin-sensitizing and hepatoprotective drugs have been subjected to study trials, but up till now, no agent has conclusively been established to prevent disease progression.

INTRODUCTION: Generally, non alcoholic fatty liver disease (NAFLD) appears to be a slowly progressive, with disease-related morbidity and mortality occurring in a minority of subjects. There appears to be, however, considerable difference in the course of the disease with rapid progression to end stage liver disease being reported among children, although it is unclear why this occurs [1].

Recently it has also been recognized that a substantial proportion of patients with cryptogenic cirrhosis have previously unrecognized NAFLD [2]. Sub fulminant liver failure is a rare presentation of NAFLD, but has been reported in patients with presumed unrecognized cirrhosis who decompensate because of an unidentified insult [3].

Progressive fibrosis comes out to be more common among patients with NASH compared to those with simple steatosis. Approximately one third of patients with NASH will have progressive fibrosis over 3 to 4 years, whereas over half will progress when followed up for 6 years. The small number of patients with simple steatosis studied has revealed progressive fibrosis in only zero to 8% of patients after a maximum of 16 years follow-up.

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Diabetes and obesity are independent risk factors for progressive fibrosis among patients with NAFLD but appear to account for a small proportion of the risk [4]. Among patients with NAFLD from tertiary referral centres followed up for a mean of 8 years, the incidence of cirrhosis is 20%, the incidence of HCC is 1%, and the incidence of liver-related death is 9% [5].

Significantly, NAFLD is associated with an increased risk of overall death compared to the general population (standardized mortality ratio 1.34), with diabetes and cirrhosis being risk factors for death [6]. Studies examining outcomes of patients with NASH have had relatively small patient numbers (32 to 42 subjects) and modest follow-up (3.8 to 5.9 years) [7]. Among these patients who were recruited from tertiary hospital centres, the occurrence of cirrhosis and liver-related death was 5% to 8% and 2% to 8%, respectively. In addition to leading to liver-related morbidity and mortality, there is some suggestion that NAFLD may put forth metabolic effects. Although insulin resistance may lead to hepatic steatosis, the presence of hepatic fat worsens hepatic insulin resistance and therefore may precipitate a vicious cycle [8].

Epidemiology: The occurrence of NAFLD is around 20–30% in the general population. With a rapid enhance in the risk factors for metabolic syndrome, NAFLD has become the most common cause of liver disease in Western countries.

Non-alcoholic fatty liver disease (NAFLD) represents a spectrum of disorders characterized by predominantly macro vesicular hepatic steatosis occurring in individuals in the absence of important alcohol consumption. In this context it is possible to distinguish a condition of simple fatty liver, where the only histologic finding is the presence of steatosis, from a state of non-alcoholic steatohepatitis (NASH), showed by hepatocellular injury/inflammation with or without fibrosis.

NAFLD is considered the hepatic manifestation of insulin resistance (IR) [9]. NAFLD is strongly associated with obesity, insulin resistance, hypertension and dyslipidaemia and is now regarded as the liver manifestation of the metabolic syndrome. Rapid increase of the obesity 'pandemic' in adults and children, coupled with the realisation that the results of obesity-related liver disease are not entirely benign, has led to rapid growth in clinical and basic studies in NAFLD [10].

NAFLD may be branded as primary or secondary depending on the underlying pathogenesis (Table 1). Primary NAFLD occurs most usually and is connected with insulin- resistant states, such as diabetes and obesity, and will be the focus of this review. Other situations associated with insulin resistance, such as polycystic ovarian syndrome and hypopituitarism, have also been described in association with NAFLD, although the exact prevalence and significance in these conditions remains unclear [11].

TABLE 1: PRIMARY OR SECONDARY NAFLD DEPENDING ON THE UNDERLYING PATHOGENESIS

Type	Particulars
Primary	Obesity, glucose intolerance, hypertension, hypertriglyceridemia, low HDL cholesterol
Secondary Drugs	Corticosteroids, tamoxifen, diltiazem, aspirin, HAART, valproate, amiodarone, methotrexate, total parental nutrition
Viruses	Hepatitis C, human immunodeficiency virus
Metabolic conditions	Hypobetalipoproteinemia, lipodystrophy, hypopituitarism, hypothalamic obesity, Weber-Christian syndrome, acute fatty liver of pregnancy, Reyes syndrome
Toxins	Organic solvents, mushroom toxins
Nutritional	Rapid weight loss, intestinal bypass surgery, starvation

NAFLD = non-alcoholic fatty liver disease; HAART = highly active antiretroviral therapy

The occurrence of NAFLD varies according to the sensitivity of the instrument used to detect hepatic steatosis. Magnetic resonance spectroscopy (MRS) and liver biopsy are the most sensitive techniques at detecting hepatic steatosis, whereas the sensitivity of ultrasound differs between 49% and 94%, being less sensitive with milder degrees of hepatic steatosis or with higher levels of body mass index (BMI) [12]. Abnormal liver enzymes not due to alcohol, viral hepatitis, or iron overload are present in 2.8% to 5.5%

of the U.S. general population and may be because of NAFLD in 66% to 90% of cases [13]. However, increased liver enzymes are insensitive at detecting NAFLD, being normal in up to 78% of cases and thus are of limited value for determining prevalence [14].

NAFLD is very common and found in persons of all ages and ethnic groups. A large population-based study of 2287 adult subjects from the United States found the adjusted occurrence of hepatic steatosis as detected by MRS to be 34%, over 90% of which could be attributed to non-alcoholic causes [14].

Overall, hepatic steatosis was slightly more common among males than females with a 1.1:1 ratio, although this amplified to 1.8:1 among Caucasians. Potential living liver transplant donors undergoing work-up with liver biopsy have a comparable prevalence of hepatic steatosis of 33% [15].

Other population-based studies have found the occurrence of hepatic steatosis or NAFLD to be between 13% and 26%. Potential reasons for the variable occurrence include the use of less sensitive imaging techniques and differences in ethnic composition and metabolic risk factors. Among Asian populations, the prevalence of NAFLD/fatty liver as detected by ultrasound is 14% to 16% [16]. Using MRS, the occurrence of fatty liver is highest among Hispanic persons (45%) compared to Caucasians or African Americans (33% and 31%, respectively) [14].

The significance of metabolic factors has been demonstrated in a population-based study from northern Italy where the prevalence of NAFLD, as determined by ultrasound, increased from 16.4% among individuals of normal weight (BMI: 25 kg/m^2) to 75.8% among obese persons (BMI 30 kg/m2). The occurrence among morbidly obese individuals undergoing bariatric surgery is up to 96% [17].

Likewise, the prevalence of NAFLD rises with increasing degrees of hyperglycemia, being 27% among subjects with normal fasting glucose levels (110 mg/dL) and rising to 43% among those with impaired fasting glycemia (110–126 mg/dL) to 62% among patients with newly diagnosed diabetes (126 mg/dL) [18]. An additional Chinese study found fatty liver to be most prevalent (28.4%) among 60- to 69-year-olds [16].

The only population-based study among children documented an occurrence of 2.6%, as determined by ultrasound, among 4- to 12-year-olds, which increased to 22% in the presence of obesity. There are no population-based epidemiological studies examining the elderly, although a frequency of NAFLD of 46% has been documented among hospitalized octogenarians. An autopsy study of 351 individuals revealed NASH in 2.7% of normal-weight subjects, which enlarged to 18.5% among obese subjects [19].

Pathophysiology: Accumulation of hepatic triglyceride results when lipid influx and de novo synthesis exceeds hepatic lipid export and utilization. Insulin resistance is a vital driving force, which promotes lipolysis of peripheral adipose tissue which in turn increases free fatty acid (FFA) influx into the liver. Hyperinsulinemia and hyperglycemia also promote *de novo* lipogenesis as well as indirectly inhibit FFA oxidation. Lipid export from the liver may also be impaired among individuals with NAFLD because of defective incorporation of triglyceride into apolipoprotein carrier proteins [20].

The exact mechanisms promoting progressive liver injury are not well defined, although substrates derived from adipose tissue such as FFA, tumor necrosis factor alpha, leptin, and adiponectin have been concerned [21, 22]. Oxidative stress appears to be important, most important to subsequent lipid peroxidation, cytokine induction, and mitochondrial dysfunction. Microvascular insufficiency has also been mixed up in the exacerbation of liver injury [23].

Treatment: Patients diagnosed with NAFLD should go through evaluation and treatment of accompanying metabolic risk factors, such as obesity, glucose intolerance, and dyslipidemia in order to modify risk of morbidity and mortality from vascular disease. Treatment schemes specific for NAFLD aim to develop insulin sensitivity and modify underlying metabolic risk factors; these strategies may also be devised to protect the liver from oxidative stress and further insults. Liver transplantation may be necessary for patients with decompensated cirrhosis or liver cancer. Pharmacotherapy should probably be reserved for those patients at highest risk of developing cirrhosis, such as those with NASH, diabetes, and obesity.

Definitive treatment recommendations regarding pharmacotherapy are difficult because of the lack of adequately powered randomized controlled trials of adequate duration and with histological end points. Weight loss by dieting and exercise has been demonstrated to improve liver biochemistry and degree of hepatic steatosis [24, 25, 26, 27]. Uncontrolled series have shown improvement in liver histology with bariatric surgery [27], although very rapid weight loss can paradoxically worsen hepatic inflammation and fibrosis [24].

Insulin-sensitizing agents, such as metformin, pioglitazone, and rosiglitazone, have been shown to improve histological features of NAFLD, although in the absence of comparative control groups [28]. Vitamin E has not been shown to convincingly improve liver biochemistry or histology [29]. Other hepatoprotective and antifibrotic agents, such as betaine, pentoxifylline, and losartan, have shown promise in small pilot trials [30].

CONCLUSION: NAFLD is a common condition connected to insulin-resistant states such as obesity and glucose intolerance. The individual risk of developing disease-related morbidity and mortality show relatively low; however, the overall public health burden may be substantial, considering the high prevalence of the disease. Further natural history studies with adequate follow-up are necessary to clarify this further. In addition, research into disease pathogenesis will aid in identifying patients who are at greatest risk of progressive disease. This will also help in the appropriate identification of which patients will need potentially long-term and expensive treatment.

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