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Review

A concise review of non-alcoholic fatty liver disease

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) is the hepatic manifestation of the metabolic syndrome and the incidence of which is rising rapidly due to the increasing epidemic of obesity in both adults and children. The initial accumulation of fat followed by subsequent inflammation is central to the development of liver damage, and is critically influenced by host factors including age, gender, presence of diabetes, genetic polymorphisms and more recently by the gut microbiome. An increasing body of data suggest that NAFLD is also an independent risk factor of cardiovascular disease, which remains the commonest cause of mortality in such patients. This review focusses on the pathogenesis of NAFLD, and the evolution of new approaches to the management and treatment of NAFLD.

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is becoming an important public health concern due to the rising incidence of obesity in both children and adults. NAFLD, defined by the presence of hepatic steatosis (the presence of fat in liver parenchyma without inflammation) in the absence of excess alcohol consumption (less than 21 units in men and 14 units in women), is considered to represent the hepatic component of metabolic syndrome [1]. NAFLD represents a spectrum of disease, ranging from simple steatosis to steatohepatitis (the presence of fat in liver parenchyma with inflammation, hepatocyte ballooning and lobular inflammation) through to fibrosis and cirrhosis [2]. Simple steatosis (SS) rarely progresses to advanced disease whereas in approximately 20% of patients with non-alcoholic steatohepatitis (NASH), it progresses to fibrosis and cirrhosis over a 15 year time period [3]. Clinical progression of NAFLD has been illustrated in Fig. 1.

It is strongly associated with insulin resistance and other metabolic risk factors such as diabetes mellitus, central abdominal obesity and dyslipidaemia [4]. NAFLD is an independent risk factor for cardiovascular disease (CVD) and predicts future events, independently of other risk factors such as age, gender, low density lipoprotein (LDL) cholesterol, smoking and other features of metabolic risk factors [5–7]. NAFLD is also associated with increased risk of all-cause mortality, contributed by liver related deaths as well as non-liver related causes such as malignancy, diabetes and coronary artery disease [8].

2. Epidemiology

The prevalence of NAFLD in normal weight individuals without the presence of metabolic risk factors is reported to be around 16% [9] rising to 43–60% in patients with diabetes [10,11], 91% in obese patients undergoing bariatric surgery [12], and up to 90% in patients with hyperlipidaemia [4,13]. The prevalence of NAFLD also increases with age from less than 20% under the age of 20 to more than 40% in over the age of 60 [6] and indeed older age has been shown to be an independent risk factor for hepatic steatosis and progression to fibrosis and cirrhosis [14]. The male gender has been regarded as a risk factor for progression to NASH and fibrosis [14]. Although earlier studies suggested that ethnicity impacts on the prevalence of NAFLD [15], subsequent studies did not confirm this on multi-variant analysis [16]. Intriguingly though the link between insulin resistance (IR) [measured by homeostasis model assessment-estimated insulin resistance (HOMA-IR)] and the risk of NASH is seemingly different between Latino and non-Latino individuals [16].

Mortality is increased in patients with steatohepatitis and advanced fibrosis but not in patients without evidence of steatohepatitis and fibrosis (known as bland steatosis). A long term follow

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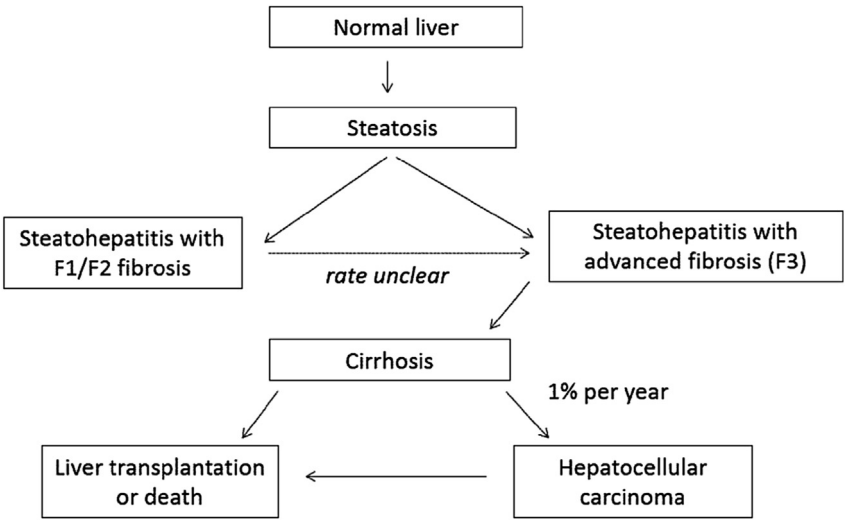

Fig. 1. Clinical progression of non-alcoholic fatty liver disease.

up study of 129 patients with biopsy proven NAFLD showed that mortality was not increased in patients with simple steatosis [17], but increased in patients with NASH. The mortality was related mainly to cardiovascular disease although liver related deaths were more common in patients with NASH cirrhosis [17]. A recent systematic review of 221 patients with biopsy proven NASH showed that patient's age and the degree of inflammation on initial liver biopsy were independent predictors of progression to advanced fibrosis whilst factors such as diabetes, hypertension and obesity were not statistically significant predictors [18]. These findings supported that the presence of advanced fibrosis was associated with increased overall mortality [19], most likely from cardiovascular events [19].

Hamabe et al. demonstrated in a retrospective study over a 10 year period that smoking was an independent risk factor for NAFLD irrespective of the presence of other metabolic risk factors [20]. Notably, the rate of development of NAFLD was similar in those individuals that stopped smoking to those that carried on, perhaps related to subsequent weight gain in individuals after cessation of smoking [20]. Modest alcohol consumption (one alcoholic beverage per day) had not been demonstrated to increase the prevalence of NAFLD, and in the case of modest wine consumption it would appear to reduce the incidence [21].

3. Natural history and pathogenesis of NAFLD

The natural history and the pathogenesis of NAFLD is not clearly well described. In NAFLD, simple steatosis is regarded as the presence of fat in <5% of hepatocytes [22] and in about 20–25% of cases, it progresses to NASH and of these patients with NASH, 20% will develop fibrosis and subsequently cirrhosis [3]. The mechanisms involved in the progression of steatosis to NASH are complex and not completely understood although increased visceral adiposity and insulin resistance (IR) with increased free fatty acids (FFA) release might play a role in the development of liver steatosis [22]. In healthy subjects, insulin stimulates hepatic as well as peripheral glucose uptake and suppress hepatic glucose production [23] whereas in the fasting state, the liver becomes the major site of glucose production as mediated by gluconeogenesis and glycogenolysis [2,24]. In patients with IR, hepatic auto-regulation is disrupted and therefore, both gluconeogenesis and glycogenolysis are increased resulting in the development of hyperglycaemia [13]. The mechanism of the liver injury in NAFLD is currently thought to be a 'multiple hit process' involving IR, oxidative stress, apoptosis and perturbations of adipokines levels [25].

3.1. Two hit hypothesis

The current model of 'two hit hypothesis in NAFD' was proposed in 1998 by Day et al. [26]. The first hit reflects the accumulation of triglycerides (TG) and FFA in hepatocytes which is a consequence of IR, enhanced dietary influx and increased hepatic lipogenesis [26]. The second hit involves lipid peroxidation, mitochondrial dysfunction and inflammation which results in hepatocyte damage and development of liver fibrosis [26]. Activation of pro-inflammatory pathway is mediated by cytokine and pattern recognition receptors, including toll like receptors and these pathways emerge on two main intracellular signalling pathways, known as nuclear factor-κβ (NF- κβ) and c-Jun N-terminal kinase (JNK) [27,28]. NF- κβ activation is reported in NASH and can lead to increased transcription of many pro-inflammatory genes, whereas JNK causes IR via direct phosphorylation and degradation of insulin receptor substrate 1 (IRS1), reducing the intracellular signalling pathway downstream the insulin receptor [27]. Lipid peroxidation can promote stellate cell proliferation contributing to fibrogenesis [29], whereas reactive oxygen species (ROS) induce cytokines release from hepatocytes that lead to the initiation of various immune mediated mechanisms contributing to further liver cell injury. The combination of hyperinsulinaemia, hepatic iron and lipid peroxidation induce oxidative stress [15], which can cause mitochondrial dysfunction in NASH and contribute to TG accumulation and eventually cell necrosis [11].

3.2. Insulin resistance

Patients with NAFLD have reduced insulin sensitivity not only in muscle but also in liver and adipose tissue [30], which play a major role in the pathogenesis of NAFLD. Due to IR, the adipose tissue becomes resistant to the anti-lipolytic effect of the insulin and results in peripheral lipolysis which causes an increase delivery of FFA to the liver as well as driving de novo lipogenesis (DNL) [6,15]. In addition, lipid overload in pancreatic-B cells leads to dysregulated insulin secretion and changes in the expression of peroxisome proliferator-activated receptor-α (PPAR-α), glucokinase, the glucose