

Recent concepts in non-alcoholic fatty liver disease

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is present in up to one-third of the general population and in the majority of patients with metabolic risk factors such as obesity and diabetes. Insulin resistance is a key pathogenic factor resulting in hepatic fat accumulation. Recent evidence demonstrates NAFLD in turn exacerbates hepatic insulin resistance and often precedes glucose intolerance. Once hepatic steatosis is established, other factors, including oxidative stress, mitochondrial dysfunction, gut-derived lipopolysaccharide and adipocytokines, may promote hepatocellular damage, inflammation and progressive liver disease. Confirmation of the diagnosis of NAFLD can usually be achieved by imaging studies, however, staging the disease requires a liver biopsy. NAFLD is associated with an increased risk of all-cause death, probably because of complications of insulin resistance such as vascular disease, as well as cirrhosis and hepatocellular carcinoma, which occur in a minority of patients. NAFLD is also now recognized to account for a substantial proportion of patients previously diagnosed with 'cryptogenic cirrhosis'. Diabetes, obesity and the necroinflammatory form of NAFLD known as non-alcoholic steatohepatitis, are risk factors for progressive liver disease. Current treatment relies on weight loss and exercise, although various insulin-sensitizing medications appear promising. Further research is needed to identify which patients will achieve the most benefit from therapy.

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Keywords cirrhosis, diabetes, non-alcoholic fatty liver disease, obesity

Abbreviations ALT, alanine aminotransaminase; ApoB, apolipoprotein B; AST, aspartate aminotransaminase; BMI, body mass index; CI, confidence interval; FFA, free fatty acids; GGT, γ glutamyltransferase; HCC, hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; OR, odds ratio

Introduction

Hepatic steatosis not because of excessive alcohol consumption is termed non-alcoholic fatty liver disease (NAFLD) and is usually associated with insulin resistance and features of the metabolic syndrome. Less commonly, NAFLD may be as a result of secondary causes such as medications (e.g. corticosteroids, methotrexate, amiodarone, tamoxifen), nutritional causes such as rapid weight loss or total parental nutrition or metabolic diseases such as lipodystrophy or dysbetalipoproteinaemia.

Histologically, NAFLD may manifest as bland hepatic steatosis or may be accompanied by hepatocellular damage plus inflammation and/or fibrosis, which is termed non-alcoholic steatohepatitis (NASH). Correspondingly, NAFLD may present as a spectrum of disease from asymptomatic steatosis with or without elevated liver aminotransaminases, or as cirrhosis with complications of liver failure and hepatocellular carcinoma.

Epidemiology

NAFLD is very common in the general population and may affect any age and ethnic group. A recent population-based study performed in the USA demonstrates that up to 34% of

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the adult general population have excessive fat accumulation in the liver, mostly unrelated to alcohol abuse [1]. This suggests that over 60 million adult Americans have NAFLD. This alarming prevalence of NAFLD is most likely as a result of the increasing prevalence of obesity, Type 2 diabetes and the metabolic syndrome in the general US population. This high prevalence of NAFLD, however, is not exclusive to the white western population. In this issue of the journal, Jimba *et al.* [2] using liver ultrasonography report a prevalence of NAFLD of 29% among healthy Japanese adults, indicating that NAFLD has reached epidemic proportions in different populations around the world. The overall prevalence of NAFLD in children is 2.6%, but increases up to 53% in obese children [3,4].

NAFLD and the metabolic syndrome

Over 90% of patients with NAFLD have at least one feature of the metabolic syndrome [5], with approximately one-third having the complete syndrome [defined as three of either: central obesity, impaired fasting glucose, hypertriglyceridaemia, low high-density lipoprotein (HDL) cholesterol and hypertension]. The likelihood of NAFLD increases as the number and severity of metabolic risk factors increase [5]. The prevalence of NAFLD in obese individuals is 76% as compared with 16% in non-obese individuals [6]. In the study by Jimba *et al.* [2], the prevalence of NAFLD increased from 27% in subjects with normal fasting glucose to 43% in those with impaired fasting glycaemia and to 62% in patients with newly diagnosed diabetes. In that study [2], body mass index (BMI), triglyceride, total cholesterol and fasting plasma glucose were independently associated with NAFLD in non-diabetic individuals.

The metabolic syndrome in NAFLD patients increases the likelihood of severe disease, conferring an odds ratio (OR) of 3.2 [95% confidence interval (CI) 1.2–8.9] for the presence of NASH and 3.5 (95% CI 1.1–11.2) for advanced fibrosis [5]. Diabetes and obesity increase the risk (1.5–4.0-fold) of hepatocellular carcinoma in the general population, most likely as a consequence of advanced NASH [7].

Pathogenesis and pathophysiology

The exact mechanisms leading to hepatic triglyceride accumulation and subsequent hepatocellular damage are incompletely understood. Insulin resistance is clearly important, acting to increase free fatty acid (FFA) influx into the liver, driving hepatic triglyceride production. Hyperinsulinaemia and hyperglycaemia also promote *de novo* lipogenesis by up-regulating lipogenic transcription factors such as sterol regulatory binding protein-1c (SREBP-1c) and carbohydrate response element binding protein [8,9]. Furthermore, insulin-mediated activation of SREBP-1c increases malonyl-CoA which inhibits FFA oxidation, thereby favouring hepatic triglyceride accumulation [9]. Lipid export from the liver may be impaired because of defective incorporation of triglyceride

into apolipoprotein B (apoB) or reduced apoB synthesis or excretion [10,11].

Hepatic triglyceride accumulation subsequently leads to hepatic insulin resistance by interfering with tyrosine phosphorylation of insulin receptor substrates 1 and 2 [12,13]. This may exacerbate overall insulin resistance, potentially explaining why patients with NASH are more insulin resistant than age-, gender- and BMI-matched control subjects [14]. In addition, hypertransaminasaemia because of NAFLD chronologically follows weight gain but precedes glucose intolerance [15].

Interestingly, Targher *et al.* report in this journal that patients with Type 2 diabetes and NAFLD, compared with those without NAFLD, have a subtle hypothalamo-pituitary-adrenal (HPA) axis disturbance manifested by increased urinary cortisol excretion and reduced cortisol suppression by dexamethasone [16]. This may be as a result of the presence of increased amounts of visceral adipose tissue which, compared with subcutaneous fat, has higher activity of 11 β -hydroxysteroid dehydrogenase resulting in increased conversion of inactive cortisone to active cortisol [17]. Other hormonal disturbances may also play a role, with rapidly progressive NAFLD noted among patients with hypopituitarism and/or hypothalamic disease, although the pathogenic mechanisms for this are unclear [18].

Hepatic lipid accumulation does not universally result in hepatocellular injury, indicating that additional secondary insults are important [19]. Increased hepatic FFA oxidation can generate oxygen radicals with subsequent lipid peroxidation, cytokine induction and mitochondrial dysfunction [20]. FFA may also cause hepatocyte apoptosis which is one mechanism of cellular injury in NAFLD patients [21,22]. Genetic polymorphisms, gut-derived bacterial lipopolysaccharide and increased fat mass may increase levels of pro-inflammatory cytokines such as tumour necrosis factor α [22–24]. Insulin sensitizing and potentially hepatoprotective cytokines such as adiponectin may be inappropriately low among NASH patients [25]. Recently, microvascular insufficiency as a result of architectural distortion from swollen lipid-laden hepatocytes and fibrosis has been implicated to impair hepatocyte oxygen and nutrient exchange leading to an inflammatory response [26].

Histology

Histological confirmation of NAFLD requires a minimum of 5% of steatosis. Excessive alcohol consumption should be excluded as possible aetiology as the histological features of NAFLD are indistinguishable from alcoholic fatty liver. The threshold of alcohol intake required to produce hepatic steatosis and steatohepatitis is not well established, although a daily limit of 20 g (approximately two standard drinks) is commonly used. The histological distinction between NASH and simple steatosis is controversial; a recent consensus conference defined NASH as steatosis with hepatocellular ballooning plus

lobular inflammation [27], although steatosis in conjunction with typical peri-cellular/peri-sinusoidal fibrosis is also considered as NASH despite the absence of inflammatory features.

Natural history

Existing studies examining the natural history of NAFLD have relatively small numbers and originate from tertiary specialist centres, thus limiting their generalizability to the broader community. Overall, patients diagnosed with NAFLD appear to have an increased mortality rate compared with the general population [28], most likely because of complications of insulin resistance such as vascular disease and NAFLD cirrhosis.

Patients with bland steatosis without evidence of steatohepatitis have a relatively benign liver-related prognosis with 1.5% developing cirrhosis and 1% dying from liver-related causes over one to two decades [29–31]. In contrast, the liver-related death rate among patients from tertiary care centres with biopsy proven NASH is up to 11% [31]. Among all NAFLD patients, diabetes is a risk factor for liver-related death (OR 22.8, 95% CI 3.0–175.0) as well as overall death (OR 3.3, 95% CI 1.8–6.2) [32].

It is now recognized that a significant proportion of patients with ‘cryptogenic’ cirrhosis had unrecognized NASH [33], particularly as histological evidence of steatohepatitis may disappear with progression to cirrhosis [34]. Cirrhotic-stage NASH may also be complicated by hepatocellular carcinoma and accounts for approximately 13% of all cases of hepatocellular carcinoma [35]. In addition, the presence of NAFLD exacerbates the severity of liver injury as a result of other hepatotoxic agents such as hepatitis C and alcohol [36].

Clinical features

Patients with NAFLD are generally asymptomatic although may have abdominal discomfort and hepatomegaly. Liver enzymes may be normal in up to 78% of patients and thus are insensitive for the detection of NAFLD [1]. In addition, the full histological spectrum of disease may be present among patients with normal ALT levels, which therefore cannot be reliably used to exclude the presence of advanced liver disease [37]. When present, liver enzyme elevations are generally modest and restricted to alanine aminotransaminase (ALT) and aspartate aminotransaminase (AST). Clinical evaluation should focus on the presence of metabolic risk factors, as well as risk factors for advanced hepatic fibrosis such as age > 45 years, diabetes, elevated BMI and an AST/ALT ratio greater than one [38].

γ -Glutamyltransferase (GGT) levels may be above the normal range in some patients with NAFLD, but are usually below that seen in patients with alcohol-induced liver injury. In this issue of the journal, Kim *et al.* [39] extend prior observations that GGT levels, even when within the normal range, correlate significantly with the presence of several components of the metabolic syndrome. Unfortunately, the presence of

fatty liver was sought by two relatively insensitive methods such as aminotransferase levels and ultrasonography, and thus it is difficult to determine the true correlation between GGT levels and the metabolic syndrome independent of fatty liver.

Imaging studies such as ultrasound, computed tomography and magnetic resonance imaging are accurate for detecting moderate to severe hepatic steatosis. The sensitivity and specificity of ultrasound for detecting > 33% steatosis is between 60–94% and 88–95%, respectively, although falls with increasing BMI to 49 and 75%, respectively, among morbidly obese individuals [40]. Localized proton magnetic resonance spectroscopy accurately measures hepatic triglyceride content in the liver [41]. Magnetic resonance spectroscopy has the advantage over the other commonly used imaging modalities of ultrasonography, computed tomography and magnetic resonance imaging, as it is quantitative rather than qualitative or semiquantitative. However, no imaging modality is able to differentiate between the histological subtypes of relatively benign non-alcoholic hepatic steatosis or more aggressive NASH. Nor is imaging able to stage the degree of liver fibrosis [42].

Liver biopsy is able to stage the disease and thus is valuable for prognostic reasons. In addition, histological evaluation can be useful to exclude other liver disease, particularly in the setting of potential concomitant drug hepatotoxicity, elevated iron studies or positive auto-antibodies [43,44]. Importantly, monitoring disease progression or response to therapy requires a liver biopsy as aminotransaminase levels improve over time regardless of whether hepatic fibrosis progresses or improves [34].

Treatment

Treatment strategies for NAFLD aim to improve insulin sensitivity and modify underlying metabolic risk factors, or protect the liver from oxidative stress and further insults. Liver transplantation may be required for patients with decompensated cirrhosis or liver cancer. Pharmacotherapy should probably be reserved for those patients at highest risk of developing complications, i.e. those with NASH, diabetes and obesity. The lack of adequately powered randomized controlled trials of sufficient duration and with histological endpoints make definitive recommendations difficult at this time.

Diet and exercise improve liver biochemistry and hepatic steatosis [45]. Uncontrolled series have demonstrated improvement in liver histology with bariatric surgery [46], although very rapid weight loss associated with very low calorie diets (< 500 kcal/day) can worsen hepatic inflammation and fibrosis [45].

Of the insulin sensitizing agents, metformin significantly improves aminotransaminases and reduces the prevalence of the metabolic syndrome, compared with either diet therapy or vitamin E [47]. Small uncontrolled pilot trials have shown that the thiazolidinediones rosiglitazone and pioglitazone are associated with an improvement of histological features [48–50].

However, concern exists regarding hepatotoxicity as 2–5% of patients were withdrawn because of rising aminotransaminases.

Vitamin E has not been shown to convincingly improve liver biochemistry or histology [50,51]. Other hepatoprotective and anti-fibrotic agents such as betaine, pentoxifylline and losartan have shown promise in small pilot trials [45,52].

Conclusions

NAFLD affects a substantial proportion of the general population and is pathogenically associated with insulin resistance. NAFLD progresses to cirrhosis and its complications in a minority of patients, particularly those with obesity and diabetes. In addition, NAFLD is associated with metabolic sequelae such as worsening hepatic insulin resistance. Subsequently, NAFLD is associated with an increased risk of all-cause death. A diagnosis of NAFLD should prompt attention to management of metabolic risk factors. Further studies are required to identify pharmacotherapeutic agents that alter the natural history of the disease as well as to identify patients who will benefit most from treatment.

Competing interests

None declared.

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