Non-alcoholic fatty liver disease

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is a global health problem, with an estimated prevalence of 30% among adults in industrialized countries, associated with obesity and type 2 diabetes mellitus. NAFLD is defined histologically and represents a spectrum from simple steatosis to steatohepatitis, fibrosis and cirrhosis. Hepatic triglyceride droplet accumulation is considered the first feature in the natural history, which in some patients is associated with inflammation and fibrosis, through the interaction of environmental and host factors. Patients with NAFLD are generally asymptomatic and usually present with incidental findings of abnormal liver function tests or an echo-bright liver on ultrasound. A firm diagnosis is required for effective clinical management, and biopsy is frequently needed to assess disease severity. Non-invasive tests are increasingly used in clinical practice to stratify risk and prioritize liver biopsy appropriately. Treatment is focused on weight reduction through dietary modifications and exercise. Cardiovascular risk factors should be addressed and the treatment of diabetes, hypertension and hyperlipidaemia optimized. Liver-specific treatments such as vitamin E and pioglitazone have shown benefit in clinical trials, but concerns remain regarding their long-term safety. Obeticholic acid has demonstrated promise.

Keywords Cirrhosis; diabetes; insulin resistance; metabolic syndrome; NAFLD; NASH; non-alcoholic fatty liver disease; non-alcoholic steatohepatitis; obesity; steatosis

What's new?

- Better understanding of pathogenesis
  - Role of genetics
  - Contribution of the microbiome
- Non-invasive assessment of disease severity
  - Serum markers/simple scores (NAFLD Fibrosis Score, Fib-4, AST/ALT ratio)
  - Transient elastography
  - Multi-parametric MRI and MR elastography
- Liver-specific therapies
  - Vitamin E
  - Pioglitazone
  - Obeticholic acid

Non-alcoholic fatty liver disease (NAFLD) is associated with obesity and the metabolic syndrome, and is now the most common cause of liver dysfunction in developed countries. It is expected to pose a significant burden on health services in the near future.

Definition and epidemiology

NAFLD is defined histologically as the presence of lipid droplets in more than 5% of hepatocytes in the absence of other causes of fat deposition, such as excessive alcohol consumption, drugs (e.g. methotrexate) and viruses (e.g. hepatitis C). The condition represents a spectrum of pathology ranging from simple steatosis, to steatosis with inflammation and hepatocyte damage (non-alcoholic steatohepatitis; NASH) with or without fibrosis (Figure 1).

The epidemiology of NAFLD and its different sub-types is difficult to study as this would require a liver biopsy. Studies using proton magnetic resonance spectroscopy (^{1}H-MRS) to quantify intrahepatic triglycerides estimated a population prevalence of 30%.[1] Using ultrasound and biopsy for disease classification, the prevalences of NAFLD and NASH were estimated at 46% and 12%, respectively.[2]

Pathogenesis

NAFLD is driven by two main pathogenic mechanisms:

- liver fat accumulation
- development of inflammation and fibrosis.

Liver fat accumulation

Obesity and peripheral insulin resistance are key NAFLD risk factors, as they lead to changes in hepatic metabolic pathways (e.g. increased *de novo* lipogenesis and decreased β-oxidation), resulting in intrahepatic triglyceride accumulation.[3] Despite intrahepatic lipid accumulation, the majority of patients will not develop inflammation and fibrosis. In fact, animal studies suggest that hepatic lipid accumulation may be a protective mechanism.[4]

Development of NASH and fibrosis

Why some patients develop inflammation (NASH) and fibrosis is not entirely understood. This progression results from the interactions of multiple pathogenic environmental and host mechanisms or 'multiple parallel hits'.[5] An increasing sedentary lifestyle and increased consumption of trans-fatty acids and refined sugars have been implicated.[6,7] Genetic factors such as polymorphisms in the patatin-like phospholipase 3 (PNPLA3) gene are also associated with disease occurrence and progression.[8]

The roles of the gut microbiome (micro-organisms and their collective genetic material in the human gut), innate immune

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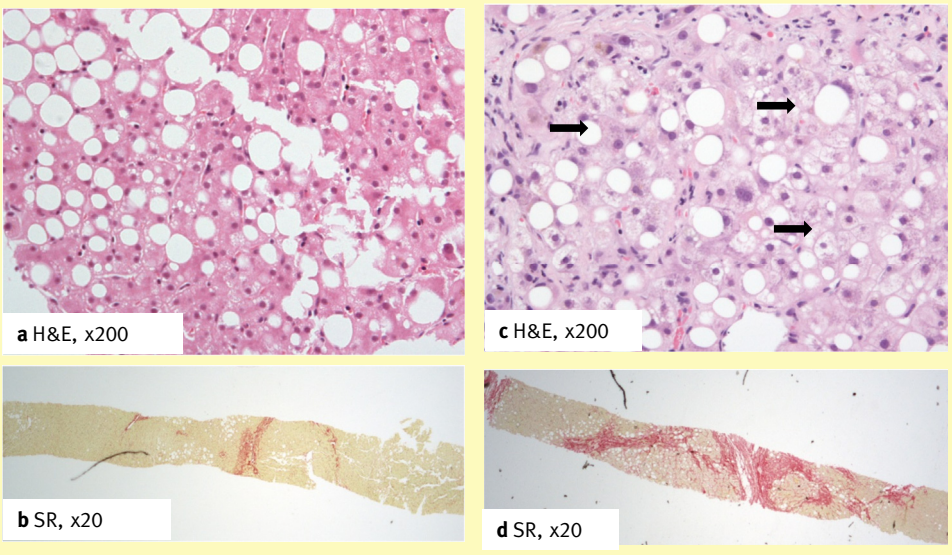
The histological spectrum of non-alcoholic fatty liver disease



The figure shows high magnification (x 200) histological sections stained with haematoxylin and eosin (H&E) from patients with **(a)** simple steatosis and **(c)** steatohepatitis, with prominent ballooning of hepatocytes (black arrows). The bottom row shows low magnification (x 20) histological sections stained with sirius red (SR) fibrosis stain from the same patients. The patient with **(b)** simple steatosis has mild fibrosis, whereas **(d)** the patient with steatohepatitis has severe fibrosis.

Figure 1

mechanisms and other gut-derived factors are increasingly being clarified. This is illustrated by the ability of gut microbiota to transfer a disease phenotype when transplanted from diseased animals to healthy controls.[9] Other pathogenic mechanisms implicated in NASH pathogenesis include endocrine factors from adipose tissue (adiponectin, leptin), cytokines (IL-6 and TNF-α) and endoplasmic reticulum stress.[5]

Natural history

Liver disease

It is generally accepted that simple steatosis confers a very low risk of progressive liver disease and that NASH and fibrosis are markers of poorer prognosis. This may be an over-simplistic interpretation of the available data, which are limited by the reliance on liver biopsy to assess for NASH and fibrosis, making the study of natural history at the population level impossible. Evidence about the long-term outcome of NAFLD comes mainly from small studies of well-characterized, histologically defined, patients.

A cohort of 129 patients with biopsy-proven NAFLD were found to have a higher mortality than the general population (84% vs 78%; $p = 0.006$) after a mean follow-up of 13.7 years. However, in subgroup analysis only patients with NASH had a higher mortality risk (80% vs 70%; $p = 0.01$), whereas those with steatosis did not.[10] A subsequent analysis of an overlapping cohort, with a mean follow-up of 26.4 years, showed that only patients with advanced stages of fibrosis (bridging) were at increased risk of all-cause mortality (hazard ratio (HR) 3.28, $p < 0.0001$) compared with the reference population,[11] whereas patients with NASH and milder forms of fibrosis (F0-2) did not have increased mortality risk (HR 1.41, $p = 0.072$). Paired biopsy studies suggest that NASH can be dynamic, with both progression and regression of disease without intervention.[12]

Patients with cirrhosis due to NAFLD are at increased risk of developing hepatocellular carcinoma (HCC). Studies estimate that 1–22% of HCC arises in patients with NAFLD.[13] In NAFLD, HCC can develop in patients without cirrhosis in 10–75% of cases.[13] Even though patients with NAFLD may be at lower risk than patients with other liver diseases (e.g. hepatitis C), the impact from HCC arising in patients with NAFLD is anticipated to be much greater because of the high prevalence of NAFLD.

Cardiovascular disease and all-cause mortality

Cardiovascular disease and malignancies are the two leading causes of death in patients with NAFLD, with liver disease in only third place. A study of 420 patients has demonstrated that patients with NAFLD have a lower overall survival compared with the background population, with 53% of mortality attributed to cardiovascular disease and malignancy, and only 13% due to end-stage liver disease.[14]

Clinical features

NAFLD is usually asymptomatic before the development of cirrhosis and complications (ascites, variceal bleeding and hepatic encephalopathy). Patients can present with non-specific symptoms such as right upper-quadrant pain or lethargy. The majority of patients are identified incidentally, through abnormal