Fatty liver

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Fatty liver is increasingly becoming more problematic from a clinical perspective. This article describes fatty liver and its clinical presentation. The current understanding of processes underlying fatty liver is reviewed, as well as the evidence for therapeutic options.

The term fatty liver covers a range of pathological changes. The basic entity that comprises fatty liver is fat deposition within hepatocytes; this is also known as steatosis. Hepatic steatosis can be seen in many settings related to alcohol, chronic hepatitis C, Wilson's disease, abetalipoproteinaemia and porphyria cutanea tarda. Many drugs can also produce hepatic steatosis; steroids, tamoxifen and amiodarone being among the most frequent offenders. The commonest cause of steatosis is non-alcoholic fatty liver disease (NAFLD) not associated with any of the above situations, and the rest of this article will concentrate on this condition.

TERMINOLOGY

NAFLD describes a spectrum of pathological changes in the liver ranging from fat alone (steatosis), through non-alcoholic steatohepatitis (NASH), to what has in the past been labelled as cryptogenic cirrhosis.

EPIDEMIOLOGY

NAFLD is recognized as being increasingly common in the western world, concomitant with the risk factors for this condition – obesity, hyperlipidaemia and type II diabetes mellitus in particular. In the UK 4% of the population has abnormal liver function tests, of which around half are thought to relate to NAFLD (unpublished data, British Association for the Study of the Liver, 2004). Data from autopsies in USA suggest a prevalence of 6.3%, with the condition found in 7–11% of liver biopsies in North America, as compared to a much lower incidence in Japan (Reid, 2001). Incidence increases with age, and with the emerging epidemic of obesity, it is felt that the prevalence of NAFLD will significantly rise.

CLINICAL FEATURES

Symptoms

Most commonly, NAFLD is asymptomatic (*Table 1*). If symptoms are present, those most frequently described include lethargy and mild right upper quadrant discomfort.

Signs

There are usually no specific abnormal signs on examination in NAFLD. The most frequently observed abnormal finding is hepatomegaly. Spider naevi has been described, and splenomegaly in up to 25% of cases. The presence of splenomegaly is unexplained, as it is not a sign of portal hypertension in the majority of these patients.

ESTABLISHING THE DIAGNOSIS

NAFLD is most frequently discovered as an asymptomatic elevation of liver function tests in an individual who has gone to see their doctor concerning another issue. The liver enzymes can show any pattern of abnormality, but alanine or aspartate transaminase (ALT or AST) levels are elevated in over 70% of cases. A raised gamma-glutamyl transferase (GGT) is also commonly found, and while an elevation of the alkaline phosphatase (ALP) can be seen, this is less frequent.

The diagnosis of NAFLD should be suspected in an individual with mildly abnormal liver function tests who has one or more features of insulin resistance, and who has no pointers to chronic viral liver disease, autoimmune liver disease or hereditary liver disease (*Table 2*). The picture can be confused by the presence of low titre anti-nuclear antibody or anti-smooth muscle antibody in a minority of patients. In a further minority

TABLE 1.
Symptoms and signs

Symptoms	Asymptomatic
	Right upper quadrant discomfort
	Fatigue
Signs	Usually none
	Hepatomegaly
	Splenomegaly
	Spider naevi
	Palmar erythema

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one can see a mild polyclonal hyperglobulinaemia, although not to a degree that suggests autoimmune liver disease. A more common finding is of raised serum ferritin. This can be found in over 50% of individuals with NAFLD (Angulo et al, 1999). The presence of an elevated ferritin is usually not associated with an increased transferrin saturation, thus demonstrating the absence of systemic iron overload. While there has been some evidence of an increased frequency of mutations in the haemochromatosis gene in patients with NAFLD and a raised ferritin, in the majority the elevation of ferritin does not correlate with stainable iron in liver biopsies, and is felt to be likely to reflect the inflammatory nature of the condition and the associated insulin resistance (Chitturi et al, 2002b).

RADIOLOGICAL EVALUATION OF NAFLD

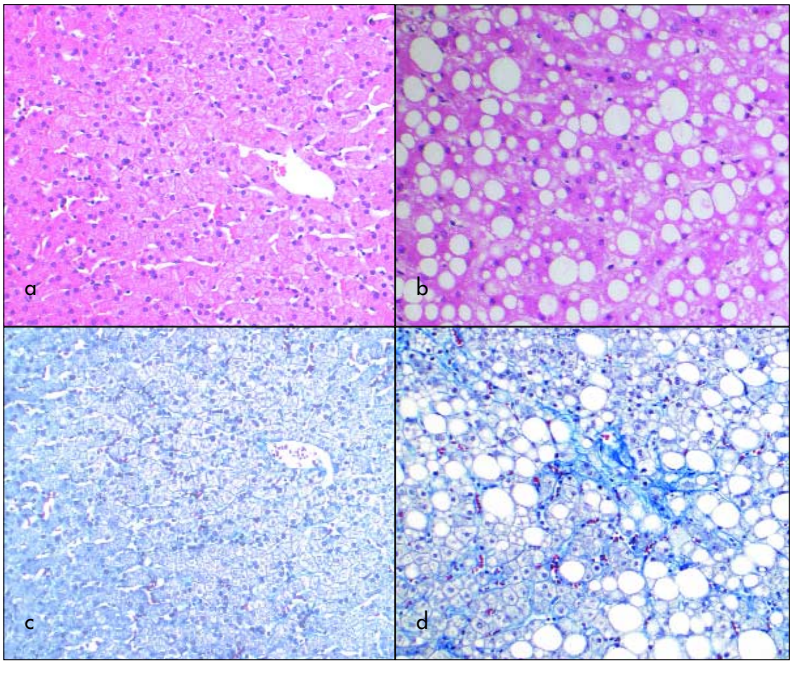
At present, the utility of radiological imaging in the assessment of NAFLD is limited. Ultrasound is good at detecting the presence of steatosis, with a sensitivity of >90%. One cannot quantify the degree of fat deposition by ultrasound, although this can be done by computed tomography or magnetic resonance imaging. Apart from the detection of steatosis, appearing as a 'bright' liver, ultrasound can also evaluate whether the liver is enlarged or appears cirrhotic, and also spleen size. The key issue in NAFLD, however, is the capability to assess the degree of scarring in the liver. That information cannot be gained from current imaging techniques, although work is ongoing into whether this may become feasible using magnetic resonance imaging.

TABLE 2.
Fatty liver and insulin resistance

Features of insulin resistance	Prevalence
Obesity (body mass index > 30 kg/m^2)	40–100%
Type 2 diabetes mellitus/impaired glucose tolerance	20–75%
Hyperlipidaemia	20–81%
Hypertension	
Biochemical insulin resistance *	98% (NASH)

* Insulin resistance as determined by the homeostasis model assessment.
NASH = non-alcoholic steatohepatitis

Figure 1. a. Normal liver. b. Fatty liver. c. Chromotrope alanine blue (CAB) stain of normal liver. d. CAB stain of non-alcoholic steatohepatitis (fibrosis shows up in blue). This shows pericellular fibrosis in a perivenular distribution.



PATHOLOGY

NAFLD remains a pathological diagnosis. There are, however, a wide variety of findings described as part of the condition. Although a scoring system has been established (Brunt staging; Brunt et al, 1999), there is a need for refinement of this as a greater understanding of the disease evolves, with more extensive experience of the pathological features seen as part of it. The basic feature is that of fat deposition within the hepatocytes. This can be large droplet (macrovesicular) or small droplet (microvesicular), and can be concentrated in the centre of the hepatic lobule around the hepatic vein (centrilobular or perivenular) or diffuse (panlobular). The presence of fat with no inflammation provides the histological diagnosis of pure steatosis.

In some liver biopsies in NAFLD, additional features are seen which can appear very similar to those of alcoholic liver injury, known as alcoholic steatohepatitis. This has led to the name non-alcoholic steatohepatitis. The features that differentiate NASH from steatosis alone are those that demonstrate inflammation: Mallory bodies (accumulations of cytoskeletal proteins), ballooning degeneration, and the presence of neutrophils and/or fibrosis. The fibrosis seen in NAFLD is most commonly centred around the hepatic vein and the hepatocytes in this zone (perivenular and pericellular), but can also be portal in some patients, without any clear evidence of a different process (*Figure 1*).

Because, as mentioned earlier, the key point of differentiation at present is between steatosis alone and NASH, liver pathologists are asked to ascribe one of these descriptions to liver biopsies in patients with NAFLD. This allows for a degree of interobserver variability on where the line is drawn, based on the interpretation of the degree of inflammatory changes and fibrosis.

NATURAL COURSE OF NAFLD

Ludwig et al (1980) first described the potential progression of disease in fatty liver over 20 years ago. Current evidence suggests that the presence of steatosis alone on liver histology confers a very low risk of future development of significant liver disease, as compared to NASH (Teli et al, 1995; Dam-Larsen et al, 2004). Given the importance of the discrimination of fat alone from NASH, there is intense interest in predicting who is at high risk of NASH on liver biopsy. Factors that have been associated with an increased risk of NASH include being over 45 years old, obesity, diabetes mellitus and hypertension (Angulo et al, 1999; Dixon et al, 2001). There is a lack of good evidence, however, on the proportion of patients with NASH who will develop progressive fibrosis or cirrhosis over a period of a number of years.

The fact that NASH can progress to cirrhosis has also been shown by indirect correlation of the prevalence of certain features of insulin resistance in NASH and in cryptogenic cirrhotics. This has lent support to the concept that a significant proportion of what is labelled as cryptogenic cirrhosis, which constitutes up to 10% of cirrhotics, is 'burnt out' NASH. Cirrhosis is known to result in an increased risk of hepatocellular carcinoma, and features of NASH are found in increased frequency in patients with hepatocellular carcinoma as well as cryptogenic cirrhosis (Bugianesi et al, 2002).

PATHOPHYSIOLOGY

It is now agreed that fatty liver is part of the insulin resistance syndrome (Chitturi et al, 2002a; Pagano et al, 2002). This is supported by the prevalence of features of this syndrome in NAFLD patients, but more rigorously by the objective demonstration of insulin resistance in 75% of patients with NASH (Chitturi et al, 2002a). The mechanism for fat accumulation in the liver as part of insulin resistance is likely to be multifactorial, with elements related to increased influx of free fatty acids to the liver from the periphery, an impaired mitochondrial capacity for the appropriate degree of fatty acid oxidation, as well as a reduction in the formation of very low-density lipoprotein (VLDL) and therefore export into the circulation. It is, as yet, unclear whether there is insulin resistance not just at the level of fat tissue and skeletal muscle, but also in the liver. Some work from insulin-resistant animal models suggest a dichotomy of insulin responses in the liver, with some, such as inhibition of gluconeogenesis, being less responsive to the presence of insulin, but others, including the activation of hepatocyte lipogenesis, being hypersensitive.

The currently favoured theory is a two-hit model in which the first insult to the liver cell is steatosis, which leads to a cell that is more sensitive to a second hit (Day and James, 1998). This second hit is thought to be an inflammatory insult, which may involve reactive oxygen species-induced damage. It remains unclear why some people develop inflammation and scarring associated with the steatosis, while others do not, as it is clear that the degree of fat accumulation does not accurately predict this.

TREATMENT

There are currently no therapies that have been proven to be of long-term histological benefit in randomized controlled studies (*Table 3*). The fundamental aspect of management of individuals with NAFLD, therefore, is lifestyle advice, in terms of increased exercise, reduction of weight through exercise and by diet, and lowering lipids through dietary modification. These are common-sense approaches to modify cardiovascular risk factors. The evidence that this is beneficial in terms of the liver is currently lacking. Treatments aimed at modifying associated risk factors have proven of some benefit, as atorvastatin has been found to improve liver enzymes in one study, at the same time as reducing cholesterol (Kiyici et al, 2003). Gemfibrozil has also been examined in this context in a small study, and been found to improve the ALT level when taken over a 4-week period (Basaranoglu et al, 1999).

Since the central problem in NAFLD is that of insulin resistance, a number of studies have looked at the effect of insulin sensitizers on the liver in this condition. Metformin is felt to sensitize the body to the effects of insulin although the mechanism is poorly defined. There is encouraging evidence that metformin taken for 4 months improves liver enzyme abnormalities and insulin sensitivity, and reduces liver size (Marchesini et al, 2001).

TABLE 3.
Potential therapies for non-alcoholic fatty liver disease

Potential therapies	Clinical results
Diet	Improved LFTs
Ursodeoxycholic acid	Improved LFTs
Vitamin E	No evidence for effect
Metformin	Improved LFTs, insulin sensitivity
Gemfibrozil	Improved LFTs
PPAR-gamma agonist	Improved LFTs, insulin sensitivity. Weight increase
HMG Co-A reductase inhibitor	Improved liver function tests
Adiponectin?	No clinical studies yet

HMG Co-A = 3-hydroxy-3-methyl-glutaryl coenzyme; LFT = liver function test; PPAR = peroxisome proliferator-activated receptor

A more recent group of agents that are known to be insulin sensitizers are the peroxisome proliferator activated receptor-gamma (PPAR-gamma) agonists, otherwise known as the thiazolidinediones (TZDs). One of the first generation of TZDs, troglitazone, was linked to rare, and occasionally fatal, hepatotoxicity. This does not seem to be a group effect of these agents, as two second-generation TZDs, pioglitazone and rosiglitazone, have not been linked with the same toxicity.

A couple of small studies have been published describing the use of these agents for NASH outside the context of diabetes (Neuschwander-Tetri et al, 2003). Over a 1-year period they appear to improve liver function tests and, more importantly, liver histology, with a reduction in inflammation and fibrosis. These agents can cause weight gain, and this was seen in a significant proportion of patients, but did not seem to affect the improvements in liver histology.

Other agents that have been tried include vitamin E and ursodeoxycholic acid (UDCA). Both have been found to improve liver function in limited studies, but a recent randomized study of UDCA found no improvement in liver histology (Lindor et al, 2004).

CONCLUSIONS

NAFLD is part of the insulin resistance syndrome, and therefore an increasingly common condition. It encompasses steatosis (fatty liver), NASH and those patients in whom NASH has progressed to cirrhosis. Once thought to be an entirely benign condition, a significant minority of people with NAFLD may develop progressive liver disease over a period of a number of years, and this risk is significantly greater in the presence of NASH. It most commonly presents as an asymptomatic mild abnormality of liver enzymes, and can only be diagnosed with certainty by liver biopsy.

There are currently no therapies that have been shown to be of benefit in NAFLD in large randomized studies, but there are encouraging early data concerning the use of insulin-sensitizing agents in this condition. Such agents should currently only be used for NAFLD in the context of clinical studies. Areas of interest for the future include a full understanding of the mechanisms underlying inflammation and fibrosis formation in this setting. Advances in this area may lead to therapies that can retard or reverse fibrosis in this and other liver diseases. **HM**

KEY POINTS

- Fatty liver (steatosis) is a pathological diagnosis.
- Fatty liver is the most common cause of abnormal liver function tests in the western world, and is increasing in incidence.
- Fatty liver has a number of causes, but the huge majority are related to insulin resistance.
- If associated with inflammation or scarring in the liver (non-alcoholic steatohepatitis; NASH), fatty liver disease can cause progressive, significant liver disease.
- Differentiation between fatty liver alone and NASH cannot reliably be made without liver histology at present.
- Non-alcoholic fatty liver disease may be responsible for a significant proportion of cases of what has been described as cryptogenic cirrhosis.
- Obesity is linked to an increased risk of cirrhosis and consequent hepatocellular carcinoma.

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Angulo P, Keach JC, Batts KP, Lindor KD (1999) Independent predictors of liver fibrosis in patients with non-alcoholic steatohepatitis. *Hepatology* **30:** 1356–62
Basaranoglu M, Acbay O, Sonsuz A (1999) A controlled trial of gemfibrozil in the treatment of patients with non-alcoholic steatohepatitis. *J Hepatol* **31:** 384
Brunt EM, Janney CG, Di Bisceglie AM, Neuschwander-Tetri B, Bacon BR (1999) Non-alcoholic steatohepatitis: a proposal for grading and staging the histological lesions. *Am J Gastroenterol* **94:** 2467–74
Bugianesi E, Leone N, Vanni E et al (2002) Expanding the natural history of nonalcoholic steatohepatitis: from cryptogenic cirrhosis to hepatocellular carcinoma. *Gastroenterology* **123:** 134–40
Chitturi S, Abeygunasekera S, Farrell GC et al (2002a) NASH and insulin resistance: insulin hypersecretion and specific association with the insulin resistance syndrome. *Hepatology* **35:** 373–9
Chitturi S, Weltman M, Farrell G et al (2002b) HFE mutations, hepatic iron and fibrosis: ethnic-specific association of NASH with C282Y but not with fibrosis severity. *Hepatology* **36:** 142–9
Dam-Larsen S, Franzmann M, Anderson I et al (2004) Long-term prognosis of fatty liver: risk of chronic liver disease and death. *Gut* **53:** 750–5
Day CP, James OF (1998) Steatohepatitis: a tale of two "hits"? *Gastroenterology* **114:** 842–5
Dixon JB, Bhathal PS, O'Brien PE (2001) Nonalcoholic fatty liver disease: predictors of non-alcoholic steatohepatitis and liver fibrosis in the severely obese. *Gastroenterology* **121:** 91–100
Kiyici M, Gulten M, Gurel S et al (2003) Ursodeoxycholic acid and atorvastatin in the treatment of nonalcoholic steatohepatitis. *Can J Gastroenterol* **17:** 713–18
Lindor KD, Howdley KV, Heathcote EJ et al (2004) Ursodeoxycholic acid treatment of non-alcoholic steatohepatitis: results of a randomised trial. *Hepatology* **39:** 770–8
Ludwig J, Viggiano TR, McGill DB, Oh BJ (1980) Nonalcoholic steatohepatitis: Mayo Clinic experience with a hitherto unnamed disease. *Mayo Clin Proc* **55:** 434–8
Marchesini G, Brizi M, Bianchi G, Tomassetti S, Zoli M, Melchionda M (2001) Metformin in non-alcoholic steatohepatitis. *Lancet* **358:** 893–4
Neuschwander-Tetri BA, Brunt EM, Wehmeier KR, Sponseller CA, Hampton K, Bacon BR (2003) Interim results of a pilot study demonstrating the early effects of the PPAR-gamma ligand rosiglitazone on insulin sensitivity, aminotransferases, hepatic steatosis and body weight in patients with non-alcoholic steatohepatitis. *J Hepatol* **38:** 434–40
Pagano G, Pacini G, Musso G et al (2002) Nonalcoholic steatohepatitis, insulin resistance, and metabolic syndrome: further evidence for an etiologic association. *Hepatology* **35:** 367–72
Reid AE (2001) Nonalcoholic steatohepatitis. *Gastroenterology* **121:** 710–23
Teli M, James O, Burt A, Bennett M, Day C (1995) The natural history of non-alcoholic fatty liver: a follow up study. *Hepatology* **22:** 1714–19