FATTY LIVER DISEASE: STEATOSIS AND STEATOHEPATITIS

A number of liver disorders, several of which are common, are characterised histologically by the presence of fat droplets within hepatocytes.

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Steatosis describes histological changes that are restricted to the presence of fat globules alone; when steatosis is accompanied by evidence of inflammation, the term used is steatohepatitis. The distinction is clinically important in that the risk of progressive liver disease, possibly ending in cirrhosis, is very much higher in steatohepatitis than in steatosis alone, generally regarded as a fairly benign condition.

MICRO-AND MACROVESICULAR STEATOSIS

Histologically, steatosis takes one of two forms, differing in appearance, aetiology and behaviour.

Microvesicular steatosis

Microvesicular steatosis describes the accumulation of tiny droplets of fat around the mitochondria within the hepatocyte. This is a marker of severe mitochondrial injury. Microvesicular steatosis is seen in various forms of drug-induced liver injury, particularly in tetracycline and valproate toxicity, in Reye's syndrome, and in acute fatty liver of pregnancy. Microvesicular steatosis typically presents as an acute illness, often associated with rapidly progressive clinical symptoms and possibly with acute liver failure. This microvesicular fat may not lead to hepatomegaly or to characteristic changes on liver ultrasound, and the diagnosis can only be confirmed by liver biopsy. Conditions associated with microvesicular steatosis are medical emergencies and require rapid identification, removal of the cause if possible, and good supportive care for hepatitis and acute liver failure.

Macrovesicular steatosis and steatohepatitis

This pattern of steatosis is a commonly encountered type of liver injury. It is characterised by the presence of one or several large droplets of fat in the hepatocytes. These large droplets may occupy most of the hepatocyte, resulting in hepatomegaly and in changes in the density that are seen on ultrasound or computed tomography (CT) scanning.

In steatohepatitis, fat infiltration is accompanied by inflammation; typically inflammatory cells (both lymphocytes and neutrophils) in the hepatic lobules (lobular hepatitis), evidence of focal hepatocyte necrosis, portal lymphocytic inflammation and pericellular fibrosis, as well as, in more severe stages, development of fibrous bands linking portal tracts to each other or to central veins – a pre-cirrhotic appearance. A number of other characteristic features may be seen, including giant mitochondria (indicating mitochondrial damage) and Mallory bodies (aggregates of intermediate filaments in the cytoplasm resulting from hepatocyte injury). Although associated with alcoholic steatohepatitis, these are not pathognomic of alcohol alone.

The risk of progressive liver disease, possibly ending in cirrhosis, is very much higher in steatohepatitis than it is in steatosis alone, generally regarded as a fairly benign condition.

NAFLD is now believed to be a manifestation of the metabolic syndrome, characterised by obesity, hypertension, glucose intolerance and type 2 diabetes, hyperlipidaemia, increased atherogenesis and a prothrombotic state, accompanied by an increased risk of cardiovascular disease and stroke.

AETIOLOGY AND ASSOCIATIONS

The following conditions may be associated with steatosis and steatohepatitis:

- non-alcoholic fatty liver disease (NAFLD) associated with insulin resistance, obesity, type 2 diabetes mellitus and hyperlipidaemia
- alcoholic liver disease
- bariatric (weight-reduction) surgery
- nutritional and intestinal conditions, including total parenteral nutrition, rapid weight loss, starvation, malnutrition and inflammatory bowel disease
- drugs, including corticosteroids, nucleoside antiretrovirals, calcium channel blockers and amiodarone.

Two of these are common: alcoholic liver injury and NAFLD. The others are less common but should be included in the differential diagnosis.

Fatty liver is a well-known complication of excessive alcohol use. However, a series of cases of steatohepatitis in patients, mainly obese and female, who had not been exposed to alcohol was reported in 1980 and termed non-alcoholic steatohepatitis (NASH). This is now recognised as one of the commonest liver conditions, and is the subject of a vast literature and much experimental work. The term non-alcoholic fatty (NAFLD) is the preferred generic term, covering both steatosis alone and true NASH, where the steatosis is accompanied by inflammation. Since both alcohol use and NASH are common, it can be difficult to ascribe a fatty liver disease to one or the other in some people who have risk factors for NASH and use alcohol.

NON-ALCOHOLIC FATTY LIVER DISEASE

NAFLD is now recognised as a very common disorder. The remainder of this article discusses NAFLD alone, which appears to be the most common liver disease in the developed world. Its prevalence is rising along with the increasing prevalence of obesity. It is found in all ethnic groups and both sexes and is becoming increasingly common in adolescents and older children. The prevalence may be as high as 24% in some populations, and it is the commonest cause of asymptomatic abnormalities in liver function tests in patients in whom other causes have been excluded. Up to 74% of obese individuals, and one-third of patients with type 2 diabetes, may have evidence of NAFLD.

NAFLD is characterised by the accumulation of fat within hepatocytes, possibly accompanied by inflammation and fibrosis, which resembles the pattern of liver injury caused by alcohol but in which alcohol is not a factor (Fig. 1).

It is strongly associated with obesity, insulin resistance (and so with type 2 diabetes and hypertriglyceridaemia). All of these are common conditions. NAFLD is now believed to be a manifestation of the metabolic syndrome, characterised by obesity, hypertension, glucose intolerance and type 2 diabetes, hyperlipidaemia, increased atherogenesis and a prothrombotic state, accompanied by an increased

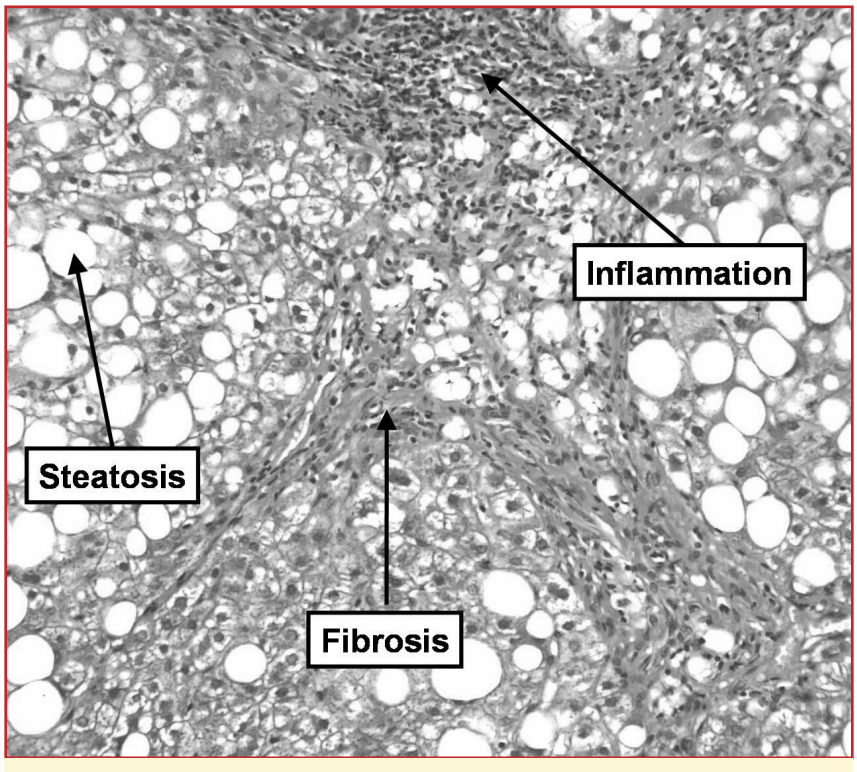

Fig. 1. Non-alcoholic steatohepatitis. Many of the hepatocytes contain large fat droplets (macrovesicular steatosis). Inflammatory cells are seen at the top of the picture and there is an increase in fibrous tissue.

risk of cardiovascular disease and stroke. By definition, the metabolic syndrome is present when any 2 of the 5 following features are present (adapted from the Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001; **285**(19): 2486-2497):

- abdominal obesity (waist circumference > 102 cm for men and 88 cm for women)
- hypertriglyceridaemia (triglycerides > 1.69 mmol/l)
- reduced HDL (men < 1.03 mmol/l , women < 1.29 mmol/l)
- hypertension (≥ 150/85 mmHg)
- fasting blood glucose (≥ 6.1 mmol/l).

Considerable evidence has accumulated to suggest that both the metabolic syndrome and NAFLD itself may result from insulin resistance. Eighty per cent of subjects with NAFLD have evidence of the metabolic syndrome.

NATURAL HISTORY OF NAFLD

Since NAFLD was recognised only fairly recently, the natural history of this slowly evolving disease is not yet fully established. It seems that NASH can progress, in a manner analogous to alcoholic steatosis, through fibrosis to cirrhosis and may be complicated by hepatocellular carcinoma. NASH is therefore a pre-cirrhotic and pre-malignant condition. In view of its prevalence, this has important public health implications. There is evidence that a proportion of patients with cryptogenic cirrhosis (cirrhosis with no obvious cause) may represent end-stage or burnt-out NASH, as, not infrequently, fully evolved cirrhosis in NASH is no longer associated with obvious fat accumulation. In general, steatosis is regarded as benign, whereas NASH is believed to be potentially progressive, with 15 - 20% of affected individuals progressing to cirrhosis.

The pathogenesis is imperfectly understood. It is not known why some patients develop inflammation and subsequently fibrosis in addition to steatosis. The 'second-hit' hypothesis is plausible: steatosis results from one insult – insulin resistance, usually as part of the metabolic syndrome – whereas a second injury is necessary to induce inflammation. Most theories accounting for the second hit invoke oxidative stress induced by one or other co-factor.

CLINICAL PRESENTATION

NAFLD is usually a silent disease. Occasionally patients may complain of some right upper-quadrant tenderness or discomfort. Fatigue and malaise may be reported. Even where inflammation is present, symptoms are usually absent. Clinical signs are few or absent. Patients are usually, but not always, obese. Hepatomegaly may be present. Only in advanced cases that have already progressed to cirrhosis will classic features of chronic liver disease be seen. Hence, cases of NAFLD are commonly detected when routine liver function tests demonstrate unexpected enzyme abnormalities. The aminotransferases AST and ALT may be elevated, usually to no more than 2 - 3 times normal. Unfortunately their correlation with the presence or absence of inflammation of the liver biopsy specimen is poor. Alkaline phosphatase is also frequently elevated. Other patients are identified by the incidental finding of imaging abnormalities on ultrasound or CT scan. Steatosis often results in hepatomegaly with an absence of diffusely increased echogenicity on ultrasound. On CT scan, however, the liver signal is attenuated.

LABORATORY INVESTIGATION

Exclude other causes of hepatitis

Take a careful drug history and consider discontinuing any drug known to be associated with hepatitis, since there is no other way to exclude this as a risk factor. Check serology for hepatitis B and C (typical viral causes of chronic hepatitis); exclude haemochromatosis with a serum ferritin and transferrin saturation; consider autoimmune hepatitis. It is occasionally necessary to exclude other common disorders such as Wilson's disease and α_1-antitrypsin deficiency. Where these other disorders have been excluded, and particularly if the patient has features of the metabolic syndrome, NAFLD becomes a highly probable diagnosis.

Investigation of the patient with suspected NAFLD

Evaluation of a patient with suspected NAFLD should be comprehensive and have 3 objectives:

- confirm that NAFLD is indeed present
- evaluate the severity of the disease, particularly with regard to inflammation and fibrosis, since these directly affect prognosis
- evaluate the effects of the metabolic syndrome itself, particularly with regard to diabetes, hypertension, hyperlipidaemia and resulting end-organ damage.

Imaging

Although ultrasound and CT scanning (Fig. 2) may be suggestive of NAFLD, they are inadequate as the sole diagnostic tests. Ultrasound has a sensitivity of 85 - 95% (slightly higher than CT scanning), but a low specificity (i.e. some patients with such a suggestive ultrasound picture will not have NAFLD). CT scanning and magnetic resonance imaging (MRI) are also sensitive for steatosis and are more specific than ultrasound. However, whatever modality is employed, a major drawback of relying on ultrasound, CT scan or MRI alone is that they *cannot* provide other vital information, such as the degree of inflammation or fibrosis (the 2 factors most predictive of a poor natural history), nor are they able to exclude other co-factors (including alcohol, iron accumulation or drug-related hepatitis) which may aggravate or be aggravated by NASH.

It must be stressed that imaging studies are not a substitute for liver biopsy where this is indicated.

Other evidence of the metabolic syndrome

Where NAFLD is suspected it is also appropriate to look for other evidence

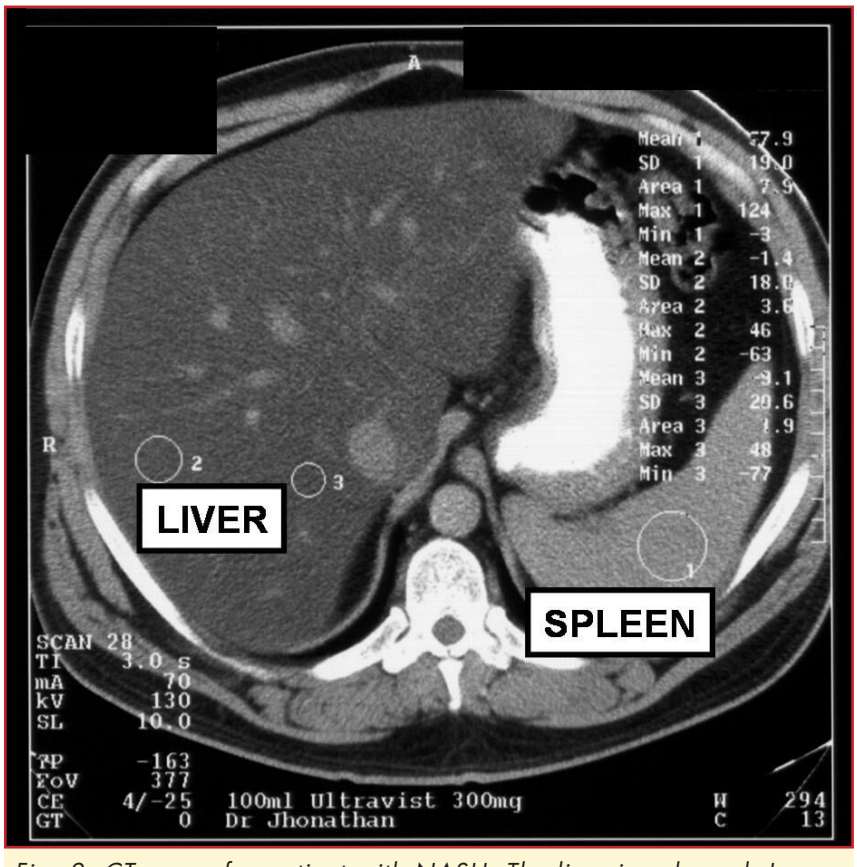

Fig. 2. CT scan of a patient with NASH. The liver is enlarged. In normal situations the liver and spleen are of the same density. Here the density of the liver (left) is clearly attenuated compared with the spleen (right).

of the metabolic syndrome, not only to strengthen the case for NAFLD, but also so that therapy for the syndrome may be undertaken. This includes a fasting glucose, lipogram and assessment of waist circumference.

Liver biopsy

Liver biopsy is the most sensitive, specific and predictive investigation. It provides a definitive diagnosis, indicates the severity of steatosis and the degree of inflammation and fibrosis, identifies any progression towards cirrhosis and is helpful in excluding other aggravating factors. A liver biopsy is not a feasible option in every patient with suspected NAFLD because of the prevalence of the condition. It is therefore necessary to have an approach that allows identification of patients who stand to benefit most from a liver biopsy. Currently we recommend that wherever NAFLD is suspected (particularly where features of the metabolic syndrome are present), the liver profile must be checked. If it is normal (aminotransferases are not elevated), it is acceptable (but not always correct) to assume that there is less likely to be major inflammation than if enzymes were elevated. The patient is then advised of practical measures that may reduce insulin resistance and therefore steatosis.

The general approach to the management of the metabolic syndrome and NAFLD is the following:

- drastically reduce or stop alcohol intake
- lose weight
- exercise
- control blood pressure
- control diabetes, preferably with metformin
- treat hyperlipidaemia
- institute any other aspect of good medical care which may be necessary.

If aminotransferases are elevated, first exclude causes of hepatitis other than NAFLD, such as hepatitis B and C using appropriate serology and haemochromatosis by demonstrating a normal transferrin saturation and serum ferritin. Drug-induced liver injury is more common than most doctors realise and can easily be responsible for an otherwise unexplained and perhaps asymptomatic elevation in aminotransferases. If the patient is exposed to any drug that might conceivably have induced injury (including self-medication with herbal and homeopathic remedies), it must be discontinued and any resultant improvement in liver enzymes noted.

Patients who have no evidence of these other liver disorders but who have features of the metabolic syndrome are likely to have NAFLD. Before proceeding to biopsy we recommend the following intensive intervention aimed at short-term reversal of transaminitis in patients who may have NAFLD:

- Exclude a drug-associated hepatitis. Take a very careful drug history, consider discontinuing any drug known to be associated with liver injury (which may include oral hypoglycaemics, lipid-lowering agents and antihypertensives) as well as over-the-counter, herbal and homeopathic remedies. This mandates a careful, patient and sympathetic history as many patients are reluctant to admit to such self-medication.
- Exclude other causes of hepatitis, including viral hepatitis and haemochromatosis.
- Begin management for the metabolic syndrome as described above.

If these recommendations result in normalisation of enzymes, it is generally not necessary to investigate further. If liver enzymes remain elevated after 3 months, liver biopsy should be done. It is not acceptable for a patient to have chronically elevated aminotransferases without a proper attempt at definitive diagnosis.

Any patient who is recognised to be atypical, more ill or more complicated requires a liver biopsy as part of the initial workup. This would include patients who have features suggestive

of autoimmune hepatitis; those who require ongoing therapy with potential hepatotoxic drugs that cannot be replaced easily; and those in whom there is a strong possibility of dual pathology (such as NASH and viral hepatitis, or NASH and haemochromatosis).

Looking for a cause for steatosis before ascribing it to NAFLD

Always exclude alcohol as a cause. There is no substitute for a careful and sympathetic history of alcohol use. This interrogation may have to be repeated. Collateral history from family members is useful. There are no laboratory tests that reliably prove alcoholic liver injury. However, a raised AST:ALT ratio, a raised carbohydrate-deficient transferrin and the presence on liver biopsy of florid features of steatohepatitis such as intense neutrophil infiltration, Mallory's hyaline and disproportionate pericellular fibrosis may be more suggestive – but not absolutely diagnostic – of alcoholic rather than non-alcoholic liver disease.

In general, where features of the metabolic syndrome are present, it is very unlikely that other disorders accounting for steatosis will be encountered. Drugs known to be associated with steatosis (such as corticosteroids, diltiazem, amiodarone and antiretrovirals) must be considered.

THERAPY

There is currently no standard specific therapy for NAFLD. Management is based on a holistic approach, which incorporates the following:

- amelioration of factors that predispose to NAFLD
- avoidance of additional factors that may aggravate liver disease
- specific pharmacological therapy.

Amelioration of factors predisposing to NAFLD

This involves correcting the insulin resistance underlying the metabolic syndrome. Encourage weight loss, and recommend a diet that can improve the atherogenic lipid profile. Weight loss should be gradual and sustained, since rapid weight loss can in its own right induce steatosis. Dietary modification must be accompanied by an appropriate exercise programme. Diabetes, hypertension and hyperlipidaemia require appropriate therapy.

Factors that may aggravate progression of the disease, such as iron overload and chronic hepatitis, must be sought and treated.

Removal of additional insults

Alcohol use must be restricted because of the effects of alcohol in promoting steatosis. Currently it is not known whether alcohol should be completely proscribed, but it would be unwise to suggest more than 2 - 3 glasses of beer or wine per week.

Specific pharmacological therapy

Drugs that increase insulin sensitivity are attractive candidates for management of the metabolic syndrome, and therefore of NAFLD. The first of these is metformin, a commonly used drug in the patient with type 2 diabetes. Preliminary studies suggest that treatment with metformin may reduce both steatosis and inflammation.

The second group are the thiazolidinediones – pioglitazone and rosiglitazone. These agents, developed for the treatment of diabetes, improve insulin sensitivity in adipose tissue. Small studies suggest that treatment with these agents may result in improvement in steatosis, inflammation and fibrosis. Paradoxically, however, treatment with the thiazolidinediones tends to result in significant weight gain: fat is redistributed from the central areas to the peripheral parts of the body. This can be cosmetically unacceptable. Additionally, some patients receiving these agents will develop a drug-induced hepatitis. Until larger trials have clarified the place and the safety of these agents in patients with NASH they should not be used for this indication alone, but preferably only as part of a clinical trial, or at least in consultation with a hepatologist.

Further reading

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IN A NUTSHELL

Fatty infiltration of the liver is a common finding on liver biopsy.

The two commonest causes for this are alcoholic liver disease and non-alcoholic fatty liver disease (NAFLD).

NAFLD is now recognised to be very common, and indeed to be the commonest liver disorder encountered in developed countries.

NAFLD is classified as steatosis (when there is fat only) and as non-alcoholic steatohepatitis (NASH) (when the fat is accompanied by inflammation and fibrosis).

NAFLD is strongly associated with the metabolic syndrome, characterised by central obesity, hypertension, glucose intolerance and an abnormal lipid profile.

The prevalence of both NAFLD and the metabolic syndrome is increasing in parallel with a developing epidemic of obesity.

NAFLD is no longer believed to be a benign disorder, but may, when associated with inflammation and fibrosis, progress to cirrhosis and even to hepatocellular carcinoma.

NAFLD may be suspected because of characteristic findings on ultrasound or CT scan or where abnormalities of the liver enzymes are determined biochemically, but is almost always asymptomatic and is frequently shown on biopsy even in the absence of these findings.

Treatment is important, but difficult, and largely revolves around attempting to reduce central obesity and therefore the features of the metabolic syndrome. Drugs that increase insulin sensitivity may improve NAFLD, but carry their own problems.