Steatohepatitis and Steatosis (Fatty Liver)

Steatosis (fatty liver) is an accumulation of fat in the liver. When this progresses to become associated with inflammation, it is known as steatohepatitis.

Fatty liver disease is divided into:

- Alcohol-related fatty liver disease.
- Non-alcoholic fatty liver disease (NAFLD).

In practical terms, it is helpful to realise the only difference between the two is the alcohol. A threshold of <20 g of alcohol per day in women and <30 g in men is usually used to allow a diagnosis of NAFLD.

When inflammation is present, this becomes non-alcoholic steatohepatitis (NASH), which can progress to cirrhosis and hepatocellular carcinoma.

NAFLD is associated with obesity, abnormal glucose tolerance and dyslipidaemia; it has been described as the hepatic manifestation of the metabolic syndrome.

As research into this spectrum of conditions remains inconclusive, there are no UK guidelines yet developed and uncertainty shrouds many important issues, including prevalence, diagnosis and treatment. Therefore, at this time the priority in management is lifestyle modification and addressing cardiovascular and metabolic risk factors.

Pathophysiology

Fatty liver (steatosis) involves the accumulation of triglycerides and other lipids in hepatocytes. This is a result of defective fatty acid metabolism, which may be caused by imbalance between energy intake and combustion, by mitochondrial damage (alcohol), by insulin resistance, or by impairment of receptors and enzymes involved.

Aetiology

Risk factors for developing fatty liver include:

- Features of metabolic syndrome: type 2 diabetes or impaired glucose tolerance, central obesity, dyslipidaemia, raised blood pressure.
- Polycystic ovary syndrome.
- Alcohol excess.
- Starvation or rapid weight loss, including following gastric bypass surgery (presumed due to sudden release of free fatty acids into the bloodstream).
- Total parenteral nutrition and refeeding syndrome.
- Hepatitis B and hepatitis C; HIV.
- Medication:
  - Amiodarone
  - Tamoxifen
  - Glucocorticoids
  - Tetracycline
  - Oestrogens
  - Methotrexate
  - Thallium
- Metabolic disorders:
  - Wilson's disease
  - Glycogen storage disorders
  - Abetalipoproteinaemia and hypobetalipoproteinaemia
  - Galactosaemia
  - Hereditary fructose intolerance
  - Homocystinuria
  - Refsum's disease
  - Systemic carnitine deficiency
  - Tyrosinaemia
  - Weber-Christian disease

Epidemiology
There is a huge variation in reported prevalence depending on the country studied, definitions and diagnostic methods used\(^2\).

- In Europe prevalence of NAFLD is estimated at 20-30% in the general population and 2.6-10% in the paediatric population\(^4\).
- In Europe prevalence of NASH is approximately 5%\(^4\).
- Fatty liver develops in 46-90% of heavy alcohol users and in up to 94% of obese individuals.
- NAFLD is the most common cause of abnormal LFTs in many developed countries.
- Incidence of NAFLD and NASH is rising in children and adolescents\(^5\).

**Presentation**

**History**
- The majority of patients with steatosis have no symptoms, although on direct questioning many patients with steatohepatitis report persistent fatigue, malaise or right upper quadrant pain.
- Advanced disease may present with symptoms of cirrhosis such as ascites, oedema and jaundice.
- Presentation is often coincidental from routine medicals and blood tests revealing abnormal LFTs (for example, raised alanine transaminase).

**Examination**
- Hepatomegaly is very common.
- Splenomegaly with or without portal hypertension may occur with cirrhosis.
- Signs of chronic liver disease may be seen in patients with cirrhosis (ascites, oedema, spider naevi).

**Differential diagnosis**
- Alpha 1-antitrypsin deficiency.
- Autoimmune hepatitis.
- Coeliac disease.
- Cirrhosis.
- Drug-induced hepatotoxicity.
- Haemochromatosis.
- Viral hepatitis in all forms.
- Hyperthyroidism or hypothyroidism.
- Primary biliary cirrhosis.
- Primary sclerosing cholangitis.
- Vitamin A toxicity.
- Wilson's disease.
- Pregnancy-related liver disease.
Investigations

A definitive diagnosis can only be achieved by liver biopsy and histopathological analysis. Efforts are being made to find non-invasive markers of disease, which can distinguish the stages of fibrosis, fibrosis from NASH and NASH from simple steatosis. However, there are no widely accepted methods at this time other than liver biopsy.

Blood tests

- LFTs: mildly raised ALT is often the first change relative to AST but this tends to reverse if disease progresses, and then ALT falls. Up to 50% of patients can have normal ALT and AST levels.
- Further LFT changes if alcohol is the cause (raised gamma-glutamyl transpeptidase (GGT)).
- Other blood tests are part of the work-up for associated causes:
  - Fasting lipids (usually raised).
  - Fasting glucose.
  - FBC.
  - Viral studies (hepatitis).
  - Iron studies.
  - Caeruloplasmin.
  - Autoimmune studies (ANA, ASMA may be raised in NASH).

Diagnostic imaging

These techniques may be used to define extent and course of disease. Steatohepatitis is usually diffuse, whereas steatosis may be focal or diffuse:

- Ultrasound:
  - Shows a hyper-echogenic, bright image.
  - Ultrasound has some diagnostic accuracy in detecting steatosis but is not good at distinguishing NASH and fibrosis within NAFLD.
- CT scanning may be helpful to monitor the course of the disease.
- MRI scan can be used to exclude fatty infiltration and the course and extent of this and other liver disease (used with phase-contrast imaging).

Biomarkers

Combinations of non-invasive biomarkers have been tested to diagnose steatosis accurately and reduce the need for liver biopsy:

- The SteatoTest®, NAFLD fibrosis score and the Kotrenen methods use differing mixes of laboratory and clinical data, calculating predictive scores from LFT ratios, serum lipids and glucose, age, sex, BMI, etc.

Liver biopsy

- This is the only definitive test. It is performed to confirm diagnosis, exclude other causes, assess extent and predict prognosis.
- Severity can be scored.

Management

This will depend on the specific diagnosis.

- Alcohol-related fatty liver is managed by abstinence and adequate diet. Abstinence can reverse alcohol-related steatosis.
- Treatment is largely aimed at the cause of the steatosis and steatohepatitis.
- The mainstay of management is weight loss (1-2 lb per week) where appropriate and control of comorbidity (blood pressure, diabetes and lipids).

There are currently no drugs licensed for NASH in the UK. USA guidelines advocate the use of vitamin E for NASH (as there is some evidence that it can improve histology) and consideration of the use of pioglitazone.

As steatosis is so common it will not be unusual for GPs to be faced with presenting features suggestive of this diagnosis and hence the need for succinct assessment and management.

A 10-minute consultation on NAFLD

- Diagnose NAFLD with confidence:
  - If the patient has classical risk factors for the metabolic syndrome.
  - If other common or treatable causes of abnormal LFTs have been excluded.
Explain:
- The abnormal liver findings (inflammation that is probably due to excess fat).
- The importance of lifestyle measures (such as gradual weight loss, regular exercise, dietary measures and alcohol cessation).
- The drug treatments for hyperglycaemia, hypertension and lipid-lowering.

Assess for the following and repeat any abnormal blood tests:
- Cardiovascular risk.
- Any hepatic complications.
- Anthropometry (including waist circumference).

Consider specialist referral where:
- There is uncertainty about the diagnosis.
- There are signs of advanced liver disease.
- There is GP or patient concern (for example, on the exact diagnosis).
- Advice about pharmacological therapies is required.

Further detail

Diet
- Gradual weight loss is important (approximately 1-2 pounds per week).
- Diets should have a high protein:calorie ratio.
- A typical low-fat diabetes-type diet is recommended.
- Abstinence from alcohol is recommended for all types of steatosis and steatohepatitis.

Exercise
- Exercise with diet increases muscle mass and increases insulin sensitivity.
- Improving cardiovascular fitness and weight training should improve NASH but, as yet, there are no randomised trials to confirm that this works in practice (the logic being that this helps reverse the underlying derangements).

Drugs
- Trials are underway to evaluate lipid-lowering agents and drugs which are insulin sensitisers.
- Improvements histologically and biochemically have been shown with thiazolidinediones, metformin (radiological and biochemical improvement), gemfibrozil (no histological data) and atorvastatin.
- Orlistat improves histological and biochemical improvements but studies are only short-term so far.

Surgery
- Bariatric surgery can bring about histological and biochemical improvements in NASH.
- Recent studies have not shown worsening hepatic function seen in earlier studies of bypass surgery (for example, gastric bypass with Roux-en-Y) in NASH.
Referral

- May be needed to a hepatologist for staging and prognosis (liver biopsy is still usually required).
- May be necessary to exclude alcohol-related liver disease, haemochromatosis, autoimmune hepatitis or where there is doubt over the diagnosis or cause.
- To a gastroenterologist or hepatologist when there are complications, such as cirrhosis or liver failure, is mandatory.

Follow-up

- All patients with chronic liver disease or at risk of disease progression should be followed up. Follow-up with the GP is appropriate. Follow-up should aim to detect any progression of disease (signs of liver disease, abnormal blood results, development of symptoms).
- Education of patients should be an ongoing process. Avoidance of alcohol and hepatotoxic drugs should be part of this.
- Promotion of gradual weight loss and an increase in exercise should continue.

Complications

- Steatohepatitis can progress to cirrhosis and liver failure just like any chronic liver disease.
- Progression to cirrhosis is more rapid when there is alcoholic liver disease or, indeed, any form of concomitant liver disease (for example, chronic viral hepatitis). Poor control of hyperlipidaemia or diabetes will also accelerate progression of fibrosis.
- Liver cancer can occur at the same rate as with other forms of liver disease.

Prognosis

The prognosis depends on the stage of disease.

Steatosis

- Has a good prognosis with abstinence and gradual weight loss.
- Cirrhosis develops in 1-2% over 20 years[15].
- Central obesity and insulin resistance are risk factors for diabetes mellitus and for cardiovascular and renal disease.

Steatohepatitis

- 10-12% of patients will progress to cirrhosis within eight years[15]. This is similar to the rate of progress towards cirrhosis in alcohol-related liver disease.

Prevention

It may be possible to prevent steatohepatitis by actively screening for patients at risk of steatosis and educating them about diet, exercise and alcohol[16].

Practice tips

- Fatty liver is not an entirely benign condition.
- At-risk patients should be identified and screened for liver disease (particularly steatosis and steatohepatitis). This will involve history, examination and blood tests but may involve further investigation if results are abnormal or the risk of liver disease is high.
- All patients at risk of steatosis or steatohepatitis should be educated about the condition (causes, management, prevention and follow-up).
- Patients with steatosis or steatohepatitis should be appropriately managed, educated and, in a few cases, referred.
- Beware of even minor abnormalities of liver function in at-risk groups.

Further reading & references

- Children's Liver Disease Foundation
- British Liver Trust
- Anstee QM, McPherson S, Day CP; How big a problem is non-alcoholic fatty liver disease? BMJ. 2011 Jul 18;343:d3897. doi: 10.1136/bmj.d3897.
- Adams LA, Angulo P, Lindor KD; Nonalcoholic fatty liver disease; Canadian Medical Association Journal, March 29 2005; 172 (7)
- Global Guidelines - Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis, World Gastroenterology Organisation (June 2012)
- Nobili V, Marcon M; Therapeutic strategies for pediatric non-alcoholic fatty liver disease: A challenge for health care providers. World J Gastroenterol. 2007 May 14;13(18):2639-41.