Steatohepatitis and steatosis (Fatty liver)

What is steatosis?

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 [1] .

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 [1] .

The priority in management is usually lifestyle modification and addressing cardiovascular and metabolic risk factors, although some patients will require referral to a hepatologist for consideration of a liver biopsy.

Pathophysiology[2]

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.

Steatosis aetiology

Risk factors for developing fatty liver include[3] [4] :

- 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.
- Obstructive sleep apnoea syndrome.
- Family history of NAFLD.
- Ethnicity - higher risk in Hispanic and Asian people, lower risk in black people.

- 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.

Steatosis epidemiology

There is a huge variation in reported prevalence depending on the country studied, definitions and diagnostic methods used [1] .

- In Europe prevalence of NAFLD is estimated at 20-30% in the general population and 2.6-10% in the paediatric population [3] .

- In Europe prevalence of NASH is approximately 5%[3] .
- 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] .

Steatosis symptoms

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 [6] . 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 [6] [7] . 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 [1] .
- 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[3] :
    - Fasting lipids (usually raised).
    - Fasting glucose.
    - FBC.
    - Viral studies (hepatitis).
    - Iron studies.
    - Caeruloplasmin.
    - Autoimmune studies (ANA, ASMA may be raised in NASH).

Non-invasive scoring systems[8]

The National Institute for Health and Care Excellence (NICE) recommends the use of the following non-invasive scoring systems to assess the risk of of advanced liver fibrosis in patients with NAFLD:

- NAFLD fibrosis score (NFS) - a score greater than minus 1.455 suggests advanced fibrosis
- Fibrosis-4 (Fib-4) - a score of greater than 2.67 suggests advanced fibrosis
- Enhanced liver fibrosis (ELF) test - a score of 10.51 or above suggests advanced fibrosis

The NFS and Fib-4 scores can be calculated in primary care with access to sufficient data - the data needed vary slightly between each test but may include transaminase levels, BMI, platelets, albumin and age. The ELF score is an algorithm which requires laboratory input and is not currently available in all areas of the UK.

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[7] .
- 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).
- The FibroScan is a non-invasive medical device that assesses liver fibrosis and cirrhosis by measuring the degree of liver stiffness. It is extensively used in secondary care - 2020 NICE briefing identified that use in primary care may save a significant number of referrals, but that there are resource implications. For instance, the cost of a FibroScan machine is £30,000 to £70,000, training (half a day) for use is needed and around the first 50 uses should be supervised by a competent user[9] .

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[10] .

Steatosis treatment and management[8] [11]

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 [12] .

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. [13] [14]

A 10-minute consultation on NAFLD [15]

- 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).
  - A non-invasive scoring system - eg, Fib-4 or NFS.
- 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).
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- A Mediterranean diet may reduce liver fat even if there is no weight loss.
- Water should be recommended instead of sugar sweetened drinks.
- Abstinence from alcohol is recommended for all types of steatosis and steatohepatitis.
- A reasonable target would be a loss of 5-10% body weight over six months.

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).
- Aim for moderate intensity exercise training for 150-200 minutes per week divided into 3-5 sessions.

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), atorvastatin and obeticholic acid.
- 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[1]

The prognosis depends on the stage of disease.

Steatosis

- Has a good prognosis with abstinence and gradual weight loss.
- Cirrhosis develops in up to 4% of people over 10-20 years[16] .
- 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.

Steatosis 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[17] .

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.

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Originally Published: 20/11/2023	Next review date: 14/03/2022	Document ID: doc_2799

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