Non-alcohol-related fatty liver disease and its primary care management

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Introduction

Non-alcohol-related fatty liver disease (NAFLD) refers to a spectrum of long-term conditions characterised by fat deposition within liver cells. It is associated with insulin resistance, diabetes, obesity and the metabolic syndrome. As a condition, NAFLD is distinct from fatty change caused by other liver disease, most particularly alcohol-related fatty liver disease.

NAFLD has a high prevalence in developed countries where it affects 20-30 % of the general population (Williams et al 2015). The prevalence of NAFLD is thought to have doubled over the past 20 years in the UK, and NAFLD may now be the most common cause of abnormal liver function tests (LFTs).

The NAFLD spectrum of disease

NAFLD encompasses liver disease from steatosis to decompensated cirrhosis:

- **Hepatic steatosis** (or 'simple non-alcohol-related fatty liver') with fat deposition within liver cells but no inflammation or scarring. This can be an incidental clinical finding on liver ultrasound scan, or may be diagnosed when abnormal liver blood tests are investigated. In most cases hepatic steatosis does not cause further liver damage. However, for some it will progress to more serious disease. In those with simple steatosis, cirrhosis may develop in up to 4% of people over 10 - 20 years, however the risk is increased if they have steatohepatitis. The risk of progression to cirrhosis in NAFLD is lower than in some other liver conditions, but because of its high prevalence, NAFLD is an increasingly important cause of advanced liver disease.
- **Non-alcohol-related steatohepatitis** (NASH)**.** Some patients with NAFLD develop NASH, a more aggressive form of liver disease characterised by inflammation and liver cell injury. The prevalence of NASH in the general population is thought to be around 2-3% (Younossi et al 2015). Approximately 12% of people with NASH progress to cirrhosis over time.
- **NASH with fibrosis**. Long-term inflammation of the liver in NASH may lead to liver fibrosis. In early fibrosis liver cell death may be minimal and damage to liver architecture small, so that liver function is preserved.
- **Hepatic cirrhosis**. This is a life-threatening, irreversible condition where inflammation has resulted in the replacement of normal liver tissue by extensive fibrosis with nodules of regenerating liver tissue. The structure and function of the liver are disrupted. Cirrhosis represents the most severe manifestation of NAFLD and is associated with decompensated liver failure, portal hypertension, hepatocellular carcinoma and death.

Most people with NAFLD, NASH and NASH with fibrosis do not have liver-specific symptoms, though some may have non-specific symptoms such as fatigue, general malaise, and upper abdominal discomfort. Even patients with NAFLD cirrhosis may remain asymptomatic until they develop liver failure.

The pathological mechanisms of NAFLD progression, and why this happens in some people but not others, are not fully understood. The average age of people with NASH is currently 40-50 years and NASH-cirrhosis 50-60 years (NICE 2016). However, prevalence studies have shown that up to 38 % of obese children now have evidence of NAFLD (NICE 2016), and, if the prevalence of obesity in children increases, the mean age that people develop significant liver disease in NAFLD is likely to fall.

However, both NAFLD and NASH are potentially reversible with lifestyle change. Early recognition allows for timely interventions and therefore opens up the possibility of preventing severe liver disease developing.

Risk factors for NAFLD

The causes of NAFLD are incompletely understood. Not everyone who is overweight develops fatty liver and not everyone who has fatty liver is overweight.

In epidemiological studies the prevalence of NAFLD is higher in those with metabolic syndrome than in the general population. Specific positive associations and predictors of NAFLD are obesity, diabetes, increased waist circumference, high triglyceride and low HDL-cholesterol (NICE 2016).

Medication such as methotrexate, amiodarone and tamoxifen may rarely be associated with fat deposition in the liver.

Diagnosing NAFLD

NAFLD is a clinical/pathological diagnosis that requires exclusion of other primary causes of liver disease. An arbitrary threshold for alcohol consumption of <20 g/day for women (2.5 units per day) and <30 g/day for men (3.75 units/day) has been adopted to exclude alcohol-related steatosis. Chronic viral hepatitis, drug-induced liver disease, haemochromatosis, Wilson's disease and autoimmune liver disease must all be excluded before NAFLD is diagnosed.

There are several challenges when considering screening for and diagnosing NAFLD.

- the high prevalence of NAFLD and its risk factors in the population
- the benign clinical course for the majority of those with steatosis
- the lack of evidence for factors that predict disease progression
- the absence of a cost-effective, sensitive and specific screening test.

Historically NAFLD has been suspected in those without known liver disease found to have abnormal liver blood tests, or who have incidental fatty changes on ultrasound. However, patients on any part of the NAFLD spectrum may have normal liver blood tests, and thus blood liver function tests have limited value in excluding NAFLD.

Liver biopsy and histology remain the diagnostic gold standard but the technique is invasive and expensive. Computed tomography (CT) may be used to diagnose fatty liver, but is expensive and represents a significant radiation burden. Ultrasound and magnetic resonance imaging (MRI) are alternative imaging options, but imaging cannot distinguish between steatosis and steatohepatitis, and ultrasound may be normal in NAFLD.

Several non-imaging, non-invasive diagnostic tests have been developed for NAFLD in adults, using a range of biomarkers. These include the Fatty Liver Index test (FLI), the SteatoTest and the NAFLD Liver Fat Score (NALFLD-LFS). Recent NICE guidance found limitations for these tests and was unable to recommend their use.

There is no evidence to support screening of asymptomatic adults with fatty liver risk factors, though NICE advises primary care clinicians to be aware that NAFLD is more common when the above risk factors exist.

NICE guidance does recommend screening children and young people for NAFLD with ultrasound scan if they have type 2 diabetes or metabolic syndrome once alcohol misuse has been excluded (NICE 2016). Those with fatty change of the liver should be referred for specialist assessment, and scans should be repeated every three years if normal. NICE NAFLD guidance is unclear on the monitoring of children with type 2 diabetes who do misuse alcohol, and refers to NICE cirrhosis guidance. However this guidance applies only to the over 16s, and it would seem prudent for all children with type 2 diabetes or metabolic syndrome to be monitored with regular ultrasound scans.

Assessing the severity of NAFLD

Once NAFLD has been diagnosed it is important to assess whether there is fibrosis and the patient is at risk of developing severe liver disease.

NICE guidance (2016) recommends using the Enhanced Liver Fibrosis (ELF) test, a proprietary blood test which combines three serum biomarkers to create an 'ELF score', to diagnose fibrosis in NAFLD. ELF testing is not available in all areas, and though not specifically recommended by NICE, alternative assessments of fibrosis include the Fib-4 test and the NAFLD fibrosis score. These use readily available serum and other biomarkers in simple algorithms to calculate indirect estimates of fibrosis risk. Transient elastography assessment of liver fibrosis can also be undertaken to triage/stage patients.

Transient elastography (TE, commonly known by the trade name 'Fibroscan') is increasingly used to detect fibrosis and diagnose cirrhosis. It is a simple, non-invasive test, similar to ultrasound

scan. Machines are available that are readily portable, and in some areas TE is available in community settings. There is no discomfort for the patient and no sedation, and the test is usually done in less than 10 minutes. It is significantly less expensive than liver biopsy, and has no unwanted effects. The results of the test are available instantly, and clinicians can share results with the patient and use them to make decisions during a routine clinic.

During TE a 50MHz sound wave is passed through the liver from a small transducer on the end of an ultrasound probe. The probe has a transducer that measures the velocity of the wave as it passes through the liver. This velocity reading is then converted into a measure of liver 'stiffness', expressed in kilopascals. Liver stiffness is a proxy measure of liver fibrosis.

Referral and monitoring in NAFLD

Some patients with NAFLD require secondary or tertiary referral. NICE guidance suggests referral of:

- children with suspected NAFLD on ultrasound scan.
- adults and young people diagnosed with NAFLD who have advanced liver fibrosis (ELF score >10.51 or other score indicating fibrosis).

Monitoring is required for those diagnosed with NAFLD who are not referred:

- children with type 2 diabetes or metabolic syndrome: liver ultrasound every three years until they reach adulthood when NICE NAFLD guidance for adults should be followed.
- adults with NAFLD but without advanced liver fibrosis (ELF score <10.51): repeat ELF test every three years.

Primary care management of NAFLD

GPs have a role in working with all patients with NAFLD, whether or not they are referred.

Lifestyle change is likely to be beneficial for all patients with NAFLD and may help either reverse, prevent or slow progression of liver disease.

Increasing exercise has been shown to reduce liver fat content, and advice on increasing physical activity, such as that given in NICE guidance 2009 for children and 2012 and 2013 for adults, is of value.

Appropriate dietary advice for people with NAFLD who are overweight or obese is summarised in NICE's obesity guidelines 2014. Dietary change is likely to be of value for all people with NAFLD, even when body mass index is normal.

Bariatric surgery may be suggested for patients who fit national criteria, and has been shown to reduce fatty liver.

Alcohol use increases the rate of NAFLD progression and patients must be encouraged to stay within national recommended limits. Those with cirrhosis should be advised to be abstinent.

The importance of other conditions in NAFLD

NAFLD, as part of a wider metabolic syndrome, is associated with a range of other conditions, and for those with NAFLD cardiovascular disease is the most common cause of death rather than liver disease. The management of NAFLD therefore must include management of related conditions.

NAFLD is a risk factor for type 2 diabetes, hypertension and chronic kidney disease and these should be screened for. In people with type 2 diabetes, co-existing NAFLD is a risk factor for atrial fibrillation and vascular disease, and these should be checked for as part of routine care.
For those with NAFLD, good management of diabetes, hypertension, hyperlipidaemia and support to stop smoking are major priorities.
Patient information

Patients with NAFLD may have unanswered questions and support needs, and can be directed to the British Liver Trust or other sources for more information.

Pharmacological and other treatments

A number of pharmacological treatments has been suggested for use in NAFLD including insulin sensitising drugs such as pioglitazone and vitamin E. No medication currently has a UK license for use in NAFLD, but there is some supportive clinical evidence for their use. NICE suggests that pioglitazone or vitamin E may be considered in secondary or tertiary care for adults with NAFLD and advanced liver fibrosis, whether or not they have diabetes. The NICE CKS page on NAFD notes that there is evidence that obeticholic acid improves the histological features of non-alcoholic steatohepatitis, including fibrosis.

Other approaches to managing NAFLD have been investigated, however NICE found no evidence to suggest that reduction in sucrose or fructose intake, omega-3 dietary supplements, or drinking caffeine in coffee protect against NAFLD progression (NICE 2016).

For useful links, please go back to the toolkit.

- NICE NG49 non-alcoholic fatty liver disease guidance (2016).
- SIGN 115 management of obesity guidance (2013).
- NICE CG189: obesity guidance (2014).
- Top ten tips non-alcohol-related fatty liver disease
- Clinical audit ideas: identification and management of NAFLD
- Toolkit resource: Personal learning reflection template
- Non-alcohol related fatty liver disease - Patient web link
- Non-alcohol related fatty liver disease patient leaflet
- British Society of Gastroenterology flowchart on the management of NAFLD

References

NICE 2009 Promoting physical activity for children and young people. NICE public health guidance 17 (2009).

NICE 2012 Walking and cycling: local measures to promote walking and cycling as forms of travel or recreation. NICE public health guidance 41 (2012).

NICE 2013 Physical activity: brief advice for adults in primary care. NICE public health guidance 44 (2013).

NICE 2014 Obesity: identification, assessment and management of overweight and obesity in children, young people and adults. NICE clinical guideline 189 (2014).

NICE 2016. Non-alcoholic fatty liver disease (NAFLD): assessment and management. NICE guideline 49 (2016)

Tsochatzis EA, Bosch J, Burroughs A. (2014) Liver cirrhosis. The Lancet. 2014; 383(9930):1749-1761

Williams R, Ashton K, Aspinall R, Bellis MA, Bosanquet J, Cramp ME et al. Implementation of the Lancet Standing Commission on Liver Disease in the UK. Lancet (London, England). 2015; 386(10008):2098-2111

Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global Epidemiology of Non-Alcoholic Fatty Liver Disease-Meta-Analytic Assessment of Prevalence, Incidence and Outcomes. Hepatology. 2015; epublication