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Be vigilant for non-alcoholic fatty liver disease in primary care

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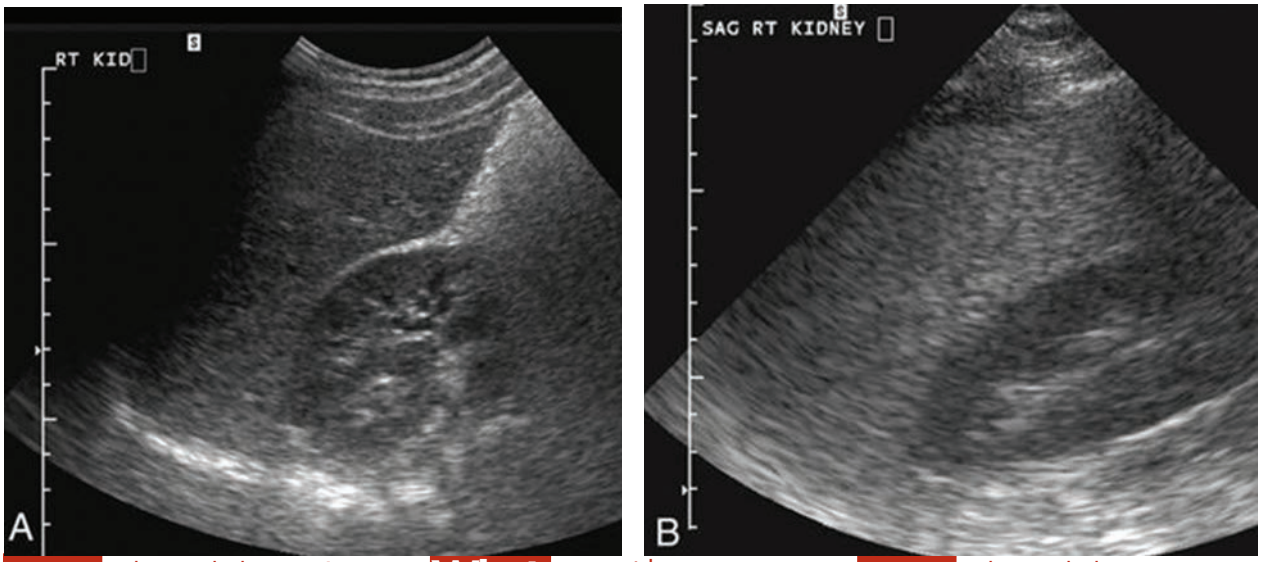

FIGURE 1
Ultrasound features in non-alcoholic fatty liver disease. **A** Normal liver demonstrates the same echogenicity as the kidney **B** Fatty liver demonstrates an increased liver echogenicity compared with the kidney

How should patients with NAFLD be assessed?

NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD) IS NOW THE MOST COMMON CAUSE OF CHRONIC LIVER disease in the Western world.[1]

A quarter of the UK population are obese and the numbers of patients being diagnosed with type 2 diabetes and other medical consequences of metabolic syndrome including NAFLD are high.[2]

Between 10 and 30% of NAFLD patients will develop non-alcoholic steatohepatitis (NASH) with a risk of progression to cirrhosis.[3] The prevalence of NAFLD is increasing and now affects approximately 20% of the global population.

RISK FACTORS

Obesity, hypertension, type 2 diabetes and hyperlipidaemia are risk factors for the development of NAFLD and NAFLD is considered to be the liver component of metabolic syndrome.[4]

As the obesity epidemic is now affecting children and adolescents we are also seeing increasing numbers with NAFLD in these populations.

Simple steatosis has not been associated with increased mortality, whereas NASH is associated with a more than ten-fold increased risk of liver-related death (2.8 vs 0.2%) and a doubling of cardiovascular risk.[3]

What are the management approaches?

At diagnosis 25-33% of patients with NASH will have advanced fibrosis, including cirrhosis.[5] In patients with advanced fibrosis at presentation, complications of cirrhosis are the third most common cause of death, following cardiovascular events and non-hepatic malignancies.

Of those with NASH and fibrosis at presentation, studies have suggested that approximately 21% of patients will have some regression of fibrosis while 38% of patients will progress over five years' follow-up.[4]

PRESENTATION

Most individuals with NAFLD are entirely asymptomatic. Blood testing for other reasons e.g. well woman/man checks often reveals mild increases in serum aminotransferases (with ALT greater than AST) and/or γ-GT. NAFLD is also often detected on routine abdominal ultrasound examination for other reasons. Occasionally hepatomegaly may be detectable clinically but the most common associated clinical findings are obesity or type 2 diabetes and a diagnosis of NAFLD should be considered in these populations.

How should patients be monitored?

DIAGNOSIS

In those suspected of, or diagnosed with NAFLD, history and clinical examination should focus on detecting features of metabolic syndrome e.g. hypertension, type 2 diabetes and hyperlipidaemia. An alcohol history is mandatory to exclude alcohol-related liver disease. However, many patients will have a combination of alcohol and non-alcohol related risk factors for their liver disease.[2]

Patients should undergo liver screening blood tests to exclude other causes of liver disease (e.g. hepatitis B and C and autoimmune causes) and an ultrasound. The presence or absence of fibrosis at diagnosis or the development of fibrosis following diagnosis are the key determinants of progression in NAFLD.[6] Fibrosis assessment therefore forms a crucial part of the patient pathway. Although routine liver blood tests may assist diagnosis of advanced »

Table 1

Lifestyle advice for non-alcoholic fatty liver disease (NAFLD)

	Advice	Potential effect
Weight loss	≥7% body weight	Reduces fatty infiltration and inflammation
Diet	Mediterranean diet	Reduces fatty infiltration
	Limit carbohydrates	Reduces fatty infiltration
	Limit fructose	Reduces risk of developing NAFLD and fatty infiltration
Activity	90-120 minutes' aerobic exercise weekly	Reduces fatty infiltration
	Strength training	Reduces fatty infiltration

liver fibrosis in patients with NAFLD (e.g. low platelet count, elevated AST: ALT ratio, Fibrosis-4 score[7]) these must not be relied upon.

FIBROSIS ASSESSMENT

GPs may have access to the enhanced liver fibrosis (ELF) blood test[6] in patients diagnosed with NAFLD to detect advanced liver fibrosis.

This biomarker-based algorithm is based on measurements of hyaluronic acid, procollagen III amino terminal propeptide and tissue inhibitor of metalloproteinase I (TIMP-1), combined. This has a high sensitivity and specificity for the detection or absence of advanced fibrosis[8] but is less effective at detecting intermediate levels of fibrosis.

Alternatively, patients may be referred to secondary or tertiary centres for assessment of hepatic stiffness using transient elastography,[9] such as FibroScan. Using an ultrasound transducer, a vibration of low frequency and amplitude is passed through the liver, the velocity of which correlates with hepatic stiffness. Stiffness (measured in kPa) increases with worsening liver fibrosis (with a sensitivity and specificity of 80-95%, compared with liver biopsy).[10] Although elastography can reliably exclude cirrhosis, it is less effective for determining lesser degrees of fibrosis.[11] It cannot be used in the presence of ascites and morbid obesity, and is affected by inflammatory tissue and congestion.[9]

Meta-analysis has shown that validated non-invasive tests for liver fibrosis consistently detect otherwise unrecognised liver disease in the general population.[12] Reliance on abnormal liver function tests will miss many patients with significant liver injury.

Given the increasing burden, the future stratification of chronic liver disease is likely to progress towards the use of non-invasive markers of liver fibrosis in the general population setting.

MONITORING AND FOLLOW-UP

Most patients can be reassured that they have little fibrosis and are also at low risk of progression. It is currently recommended that adults with NAFLD re-attend for fibrosis assessment every three years and young people under 18 every two years. No interim tests are needed. However, patients should receive advice about lifestyle modifications and any cardiovascular risk factors must be managed aggressively.

Those with an ELF score of 10.51 or above,[13] or a transient elastography score > 9, are highly likely to have significant/advanced fibrosis and must be referred to a specialist in hepatology. These tests will also be used in tertiary care to follow up those with advanced fibrosis.

OTHER CONSIDERATIONS

NAFLD is a risk factor for type 2 diabetes, hypertension and chronic kidney disease, atrial fibrillation, myocardial infarction, ischaemic stroke and death from cardiovascular causes. Statins are considered safe in patients with NAFLD and normal monitoring is required i.e. only consider stopping if liver enzyme levels double within three months of commencement, including those with abnormal baseline liver blood results.

Patients with NASH on simvastatin have shown no improvements in liver histology or enzyme levels whereas those on atorvastatin have shown improvement in both liver enzyme levels and radiological steatosis.[14] There is very limited evidence that ACE inhibitors (ACEi) may improve fibrosis. Therefore ACEi for hypertension may have an added benefit.[15]

Omega-3 fatty acids may improve radiographic steatosis but are not recommended for treatment of NASH.[16] However, they are safe to use in patients with NAFLD for the treatment of hypertriglyceridaemia.[17]

MANAGEMENT

Lifestyle

All patients with NAFLD require lifestyle advice aimed at weight loss, increased physical activity, and attention to cardiovascular risk factors, see table 1, left.[18]

Weight management programmes should include behaviour change strategies to increase physical activity levels, improve eating behaviour, the quality of the diet, and reduce energy intake. Calorie restriction is recommended (600 kcal/day deficit), aimed at losing 0.5-1.0 kg per week until the target weight is achieved. Dietary changes should be tailored to food preferences and allow for a flexible and individual approach. Unduly restrictive and nutritionally unbalanced diets should be avoided as these are ineffective in the long term and can be harmful. An improvement in diet is to be encouraged even if people do not lose weight, as there can be other health benefits.

Very low calorie diets should only be considered as part of a multicomponent weight management strategy, for people who are obese and who have a clinically assessed need to lose weight rapidly e.g. for joint replacement surgery.

A reduction of more than 7-9% in body weight has been associated with reduced steatosis, hepatocellular injury and hepatic inflammation.[19] In view of the multiplicative rather than additive nature of liver damage, the importance of staying within the national recommended limits for alcohol consumption should be strongly emphasised.

Orlistat, an enteric lipase inhibitor causing malabsorption of dietary fat, is used with a low fat diet as an adjunct in subjects with a BMI > 30 kg/m^2. [20] Only those achieving > 5% weight loss in three months should continue orlistat, and then only for a year, as fat-soluble vitamin deficiency may occur.

Patients should be encouraged to increase their level of physical activity even if they do not lose weight as a result, because of other potential health benefits e.g. reduced risk of type 2 diabetes, cardiovascular disease and reduced liver fat content. Adults should complete at least 30 minutes of moderate or greater intensity physical activity on five or more days a week.

Table 2

Pharmacotherapy for non-alcoholic fatty liver disease

Recommended treatment (under hepatologist supervision)	Dose	Patient group	Outcomes
Vitamin E	800 units/day	*NASH without diabetes	Improvement in fatty infiltration and inflammation
Pioglitazone	30-45 mg/day	NASH with diabetes	Improvement in fatty infiltration and inflammation
Potential treatments			
Omega-3 fatty acids	2-6 g/day	NASH with and without diabetes	Improvement in fatty infiltration on ultrasound, RCTs ongoing
Pentoxifylline	1,200 mg/day	NASH	Improvement in fatty infiltration
Treatments with no benefit			
Metformin	500-2,000 mg/day	NASH without diabetes or diabetes without insulin	Null
Ursodeoxycholic acid	10-35 mg/kg/day	NASH	Null
Orlistat	120 mg tds	NASH	Null

* NASH = non-alcoholic steatohepatitis

Most overweight patients may need 45-60 minutes of moderate intensity activity a day, particularly if they do not reduce their energy intake and 60-90 minutes of activity a day to avoid regaining weight. A managed approach with agreed goals that incorporate activities into everyday life as well as discouraging inactivity is the most effective strategy.

Pharmacotherapy

Less than 50% of patients are able to achieve ≥7% weight loss even in a trial setting.[21] In those with advanced fibrosis, specific liver-directed pharmacotherapy may be needed. No drugs are currently licensed specifically for treating NASH and there is an urgent need for well designed randomised controlled trials (RCTs).

In accordance with available clinical data, for those with biopsy-proven NASH in whom lifestyle intervention has failed, pioglitazone or vitamin E may be considered under specialist supervision,[22] see table 2, above. Meta-analysis data have demonstrated that pioglitazone significantly improves liver steatosis, inflammation and, to a lesser degree, fibrosis.[23] However, it is associated with weight gain and there have been reports of congestive cardiac failure, bladder cancer and reduced bone density.[24] Conversely, pioglitazone reduces death, myocardial infarction and stroke in diabetes patients. The risks and benefits to each patient should be evaluated accordingly.[25]

Vitamin E (800 IU/day) is an antioxidant that improves steatohepatitis. However, a meta-analysis showed an increase in all cause mortality at doses over 400 IU/day, and an increased risk of haemorrhagic stroke and prostate cancer has also been reported.[26]

Metformin and ursodeoxycholic acid had no effect in studies on NASH patients and there is insufficient evidence to recommend pentoxifylline.[17]

Bariatric surgery

Weight loss following bariatric surgery leads to reduced steatosis, steatohepatitis and fibrosis. There have been several uncontrolled studies demonstrating potential benefit, however the lack of RCTs precluded a Cochrane review concluding this is a validated strategy.[27] The optimum technique is unknown and long-term data are lacking, although initial concerns about worsening fibrosis do not appear to have been borne out.

Bariatric surgery should be avoided in those with advanced cirrhosis and portal hypertension, but gastric bypass and sleeve gastrectomy have led to weight loss and improved obesity-related comorbidities in Child-Pugh A cirrhosis.[28]

FUTURE DIRECTIONS

It is anticipated that emerging therapies will vastly broaden the therapeutic landscape and offer effective therapy that can alter the natural history of the disease. The farnesoid X receptor agonist, obeticholic acid, is the first new agent in which beneficial changes in liver histology have been identified. A 72-week trial of 273 patients with NASH randomised to obeticholic acid or placebo reported evidence of significant reductions in the degree of steatosis, grade of inflammation/ballooning degeneration and stage of fibrosis.[29] These changes were accompanied by mild weight loss and improved clinical biochemistry parameters, also consistent with reduced liver damage. However, a rise in total cholesterol and a disadvantageous change in high density lipoprotein: low density lipoprotein ratio were also observed with obeticholic acid. A phase III RCT is currently underway (https://clinicaltrials.gov/ct2/show/NCT02548351).

Other promising agents under investigation include a PPARα/δ agonist, caspase inhibitor, CC chemokine receptor 2/5 antagonists and glucagon-like peptide-1 agonists.[17]

CONCLUSIONS

Although now the most common cause of liver disease in primary care, NAFLD has a substantial interpatient variability in prognosis with the majority of patients never developing clinically significant liver disease and cardiovascular disease remains their primary cause of death.

Diet and lifestyle modification to aid sustained weight loss is the mainstay of therapy but to be successful requires significant input and encouragement. However, diligent management of cardiovascular risk may be more easily achieved in primary care. For patients with NASH and advanced fibrosis, current liver directed pharmacotherapy with vitamin E and pioglitazone offer potential benefit in selected patients but with potential serious adverse effects, limiting their use. Bariatric surgery appears to improve NASH but RCT »

key points

SELECTED BY

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Non-alcoholic fatty liver disease (NAFLD) is now the most common cause of chronic liver disease in the Western world. The prevalence of NAFLD is increasing and affects around 20% of the global population. A quarter of the UK population are obese and the numbers of patients being diagnosed with type 2 diabetes and other medical consequences of metabolic syndrome including NAFLD are high. Obesity, hypertension, type 2 diabetes, and hyperlipidaemia are risk factors for the development of NAFLD, and NAFLD is considered to be the liver component of metabolic syndrome.

Between 10 and 30% of NAFLD patients will develop non-alcoholic steatohepatitis (NASH) with a risk of progression to cirrhosis. Of those with NASH and fibrosis at presentation, studies have suggested that approximately 21% of patients will have some regression of fibrosis while 38% of patients will progress over five years' follow-up.

Most patients with NAFLD are entirely asymptomatic and NAFLD may be an incidental finding in primary care. Blood testing for other reasons e.g. well woman/man checks often reveals mild increases in serum aminotransferases (with ALT greater than AST) and/or γ-GT. NAFLD is also often detected on routine abdominal ultrasound for other reasons. Occasionally hepatomegaly may be detectable clinically but the most common associated clinical findings are obesity or type 2 diabetes and a diagnosis of NAFLD should be considered in these populations.

In those suspected of, or diagnosed with, NAFLD history and clinical examination should focus on detecting features of metabolic syndrome e.g. hypertension, type 2 diabetes and hyperlipidaemia. An alcohol history is mandatory to exclude alcohol-related liver disease. However, many will have a combination of alcohol and non-alcohol related risk factors for their liver disease. Patients should undergo liver screening blood tests to exclude other causes of liver disease (e.g. hepatitis B and C and autoimmune causes) and an ultrasound. The presence or absence of fibrosis at diagnosis or the development of fibrosis following diagnosis are the key determinants of progression in NAFLD.

The enhanced liver fibrosis (ELF) blood test is performed in patients who have been diagnosed with NAFLD to detect advanced liver fibrosis. Those with an ELF score of 10.51 or above, or a transient elastography score > 9, are highly likely to have significant/advanced fibrosis and must be referred to a specialist in hepatology.

Primary care management of NAFLD focuses on lifestyle change, dietary improvement, increased physical activity and weight loss together with management of associated cardiovascular risk factors. For those diagnosed with NAFLD, who do not have advanced fibrosis, assessment should be repeated every three years in adults and every two years in those under 18.

evidence is lacking. New agents currently in trial may prove efficacious but treatment duration, potential adverse effects and cost may preclude widespread use.

Competing interests: None

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