J R Coll Physicians Edinb 2020; 50: 256–61 | doi: 10.4997/JRCPE.2020.308 REVIEW

Diagnosis and management of fatty liver

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Abstract

Globally, the prevalence of non-alcoholic fatty liver disease (NAFLD) is increasing rapidly and constitutes a significant healthcare burden due to associated complications including hepatic (cirrhosis and hepatocellular cancer) and non-hepatic (cardiovascular deaths) disorders. It is closely linked to insulin resistance and metabolic syndrome but moderate alcohol consumption frequently coexists. Recently, genetic polymorphisms were implicated in the development of non-obese NAFLD. Apart from liver biopsy, in order to assess for steatosis, fibrosis and non-alcoholic steatohepatitis (NASH), advances in non-invasive serum tests and elastography have provided similarly accurate, more accessible and safer alternatives for risk stratification. As for treatment in 2020, weight loss and lifestyle modification remain the central strategy. Unfortunately, no pharmacological agents have been approved thus far, but there are a number of potential therapies in the pipeline for fibrosis and NASH. Treatment of underlying metabolic disorders is important. While the term NAFLD was coined in the 1980s, more recent understanding may support a change in nomenclature highlighting its strong metabolic roots.

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Keywords: non-alcoholic fatty liver disease, metabolic-associated fatty liver disease, non-alcoholic steatohepatitis, metabolic syndrome

Financial and Competing Interests: No conflict of interests declared

Introduction

Since 1980s, the terms NAFLD and NASH have been used by clinicians and pathologists to describe histopathological conditions similar to alcohol-associated liver disease (ALD).[1] At that time, little was known about NAFLD and NASH. Currently, NAFLD is an umbrella term that covers a spectrum of disorders from non-alcoholic fatty liver (NAFL) to NASH. NAFL is characterised by histological features in liver biopsy of hepatic steatosis with minimal lobular inflammation, while NASH has histological features of hepatocyte ballooning and marked lobular inflammation, causing late complications of fibrosis, cirrhosis and hepatocellular carcinoma (HCC).[2] While the exact aetiology is unknown, metabolic abnormalities and obesity are closely linked with NAFLD. Thus NAFLD is considered a misnomer and some groups have proposed a revision to the more aptly named term metabolic-associated fatty liver disease (MAFLD).[3]

The gene variants patatin-like phospholipase domain–containing 3 (PNPLA3), transmembrane-6 superfamily 2 (TM6SF2), sterol regulatory element-binding protein 2 (SREBP-2) and cholesterol-ester transfer protein (CETP) have been recently implicated in development and progression of non-obese NAFLD.[4] A higher degree of hepatic steatosis and a higher risk of NASH were associated with carriers of PNPLA3 I148M and TM6SF2 E167K variants.[5,6]

The prevalence of NAFLD has increased exponentially in the twenty-first century, with a current global disease burden estimated to be about 25% of the global population.[7,8] NAFLD is more prevalent in the older age group (>30 years) and in patients with type 2 diabetes mellitus.[9] Due to its preventable complications, such as progression to decompensated liver cirrhosis and hepatocellular carcinoma (HCC), it is important for physicians to correctly diagnose and treat this condition early. Bearing this in mind, our clinically-focused review aims to provide an up-to-date understanding of NAFLD, including its clinical approach and management and is especially targeted to the non-hepatologists practising in the Asia-Pacific region.

What features are important to diagnose fatty liver?

Demonstration of hepatic steatosis

Hepatic steatosis is present if total intrahepatic fat mass is ≥5% of liver mass.[10] Steatosis can be demonstrated non-invasively using various radiological modalities such as liver ultrasonography, controlled attenuation parameter (CAP) using

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Examples of alcoholic beverages	Volume (ml)	Alcohol concentration by volume (%)	Approximate alcohol content[a] (g)
Beer	330 ml	5	13
Wine	100 ml	12.5	10
Spirits e.g. whisky	45 ml	40	14

Table 1 Alcohol content of common alcoholic beverages.

[a] 10ml of pure alcohol weighs approximately 8 grams at room temperature.

elastography, or using tests based on blood investigations such as the Fatty Liver Index or Hepatic Steatosis Index in resource-constrained healthcare systems.

Looking for other common causes of fatty liver including alcohol

At baseline and during follow-up, exclusion of other causes of hepatic steatosis such as significant alcohol intake (for males >30 g/day, females >20 g/day)[2] (Table 1), drug-induced liver injury (DILI), and viral infections (human immunodeficiency virus and hepatitis C virus) are no longer a prerequisite for attaining diagnosis. Patients with NAFLD and with concomitant coexisting conditions should be grouped under the category of dual (or more) aetiology fatty liver disease. Recently, the consensus to rename NAFLD also incorporated a dual aetiology criterion for the diagnosis of MAFLD.[11]

It is important to note that moderate consumption of alcohol may predispose to NAFLD especially if metabolic risk factors are also present.[12] Progression of hepatic fibrosis in NAFLD is also associated with alcohol consumption.[13]

Establishing and assessing metabolic risk factors

Central to the pathogenesis of NAFLD is the presence of metabolic syndrome. In NAFLD patients, hepatic steatosis is frequently associated with obesity or overweight (BMI>25 kg/m^2 in the Caucasian population and >23 kg/m^2 in Asians), type 2 diabetes mellitus or presence of metabolic risk factors. (Table 2)[1,11,14,15]

Diseases related to metabolic syndrome such as accelerated atherosclerosis, type 2 diabetes and chronic kidney disease are more common among patients with NAFLD,[16,17] thus these disorders should be assessed in detail. It is important to note that cardiovascular disease is the main cause of mortality in this group of patients, followed by liver morbidity and cancer.[18]

Table 2 Metabolic risk factors

1. Waist circumference ≥102/88 cm in Caucasian men and women or ≥90/80 cm in Asian men and women
2. Elevated blood pressure ≥130/85 mmHg or taking antihypertensive medication(s)
3. Impaired fasting blood glucose = 100 to 125 mg/dl (5.6 to 6.9 mmol/l)
4. Hypertriglyceridemia ≥ 150 mg/dl (1.7 mmol/l)
5. Decreased HDL-cholesterol levels< 40 mg/dl (1.0 mmol/l) in men or < 50 mg/dl (1.3 mmol/l) in women
6. Inflammation with elevated serum high-sensitivity C-reactive protein level
7. Homeostasis model assessment - insulin resistance (HOMA-IR) score ≥ 2.5.[a]

[a] HOMA-IR formula: fasting insulin (μU/L) x fasting glucose (nmol/l)/22.5.

Looking for unhealthy dietary habits and assessing for obesity

High dietary saturated fats, high-calorie foods and intake of refined carbohydrates including fructose have been associated with NAFLD.[19] A sedentary lifestyle is also implicated as a risk factor.[20] BMI and waist circumference (measured midpoint from the lower margin of the last palpable rib to the top of the iliac crest)[21] are well validated and simple tests that can easily be performed. Waist circumference is an excellent anthropometric predictor of visceral fat and is as good as BMI for assessing total body fat. Bioimpedance, densitometry, CT scan and MRI for body fat estimation are mainly used in clinical research.[22]

Screening for liver complications

Patients with NAFL or NASH may progress to develop hepatic fibrosis, where on average, one fibrosis stage progression was documented over 14.3 years for NAFL and 7.1 years for NASH respectively.[23] Progressive fibrosis may lead to eventual liver cirrhosis (previously recognised as cryptogenic cirrhosis), hepatic decompensation and later HCC. Male sex, metabolic syndrome, obesity, type 2 diabetes mellitus and iron overload are recognised risks for developing HCC in NAFLD.[24] Patients with NASH have an increased risk of fibrosis progression and development of liver cirrhosis which can lead to decompensated liver cirrhosis.[25] A closer follow-up interval and more intensive treatment is thus needed for those with NASH. A matter of greater concern is that HCC may develop even in the absence of liver cirrhosis.[2] In the United States, NASH is now the leading indication for liver transplantation and the second most common cause for HCC.[26]

Screening for complications of liver cirrhosis, namely gastroscopy for oesophageal and fundal varices and ultrasound and alpha-fetoprotein monitoring for HCC surveillance needs to be performed at regular intervals.[27]

How to assess fatty liver

Identifying who has fatty liver

Initial assessment from history taking should include quantification of alcohol intake, drug history and fluctuations of body weight. It should also identify comorbidities, including type 2 diabetes mellitus, hypertension and cardiovascular diseases. BMI, blood pressure and waist circumference should be documented. Liver enzymes, namely aspartate

Table 3 Sensitivity and specificity of non-invasive imaging assessment of hepatic steatosis[a]

Technique	Sensitivity %	Specificity %
Ultrasound	85.2	85.2
Computed tomography	72.0	94.6
Controlled attenuation parameter	78.0	79.0
Magnetic resonance spectroscopy	97.4	76.1

[a] Compared with liver biopsy

Table 4 Assessment of hepatic fibrosis by non-invasive imaging: comparison with liver biopsy

Technique	Sensitivity %	Specificity %
Ultrasound (for cirrhosis)	91.1	93.5
Transient elastography		
For F2 fibrosis	67-88	61-84
For F3 fibrosis	65-100	75-93
For F4 fibrosis	78-100	82-98
Magnetic resonance elastography (F3 to F4 fibrosis)	85.4	88.4

transaminase (AST), alanine transaminase (ALT) and gamma-glutamyl-transpeptidase (GGT) should be assessed at baseline and during follow-up when clinically indicated. Screening for prediabetes and diabetes, insulin resistance with HOMA-IR score, dyslipidaemia, and hyperuricemia should be performed upon diagnosis of NAFL. Exclusion of viral hepatitis, autoimmune hepatitis, haemochromatosis, coeliac disease, thyroid diseases, polycystic ovary syndrome, Wilson disease and α1-antitrypsin deficiency may be performed in selected patients depending on context and clinical indications.[2]

Investigating a patient with fatty liver

Liver histology is currently the gold standard to differentiate NAFL from NASH as well as to investigate for other causes of fatty liver or fibrosis.[2] Of note, hepatic steatosis can be present in various liver diseases and not a specific finding to any liver disease in particular. Also, liver biopsies for histological examination are not 100% accurate, as other pathologies may be missed. Complications of ultrasound-guided percutaneous liver biopsy include significant bleeding at the biopsy site (1 in 500) and death (1 in 10,000).[28]

As liver biopsy is invasive, non-invasive tests using blood investigations and imaging methods offer a safer and similarly accurate assessment of NAFLD, especially regarding steatosis and fibrosis. This however, comes at the expense of specificity. In assessing steatosis, liver ultrasonography remains the initial modality of choice due to its wide availability and low costs. In tertiary centres, CAP and MRI spectroscopy are other imaging modalities to aid diagnosis of NAFLD with the additional benefit to quantify hepatic steatosis objectively (Table 3).[2,29,30,31]

Ultrasound is widely available for the assessment of liver cirrhosis. Earlier stages of liver fibrosis (<F4) can be detected by serum fibrosis markers or elastography (Table 4).[2,32,33] Serum fibrosis markers include NAFLD fibrosis score (NFS), fibrosis 4 calculator (FIB-4), enhanced liver fibrosis (ELF) and Fibro-Test®. NFS and FIB-4 have been validated in multi-ethnic populations and are freely available online calculators based on routine laboratory tests (Table 5).[2,34,35] Elastography is superior to serum markers to assess fibrosis and particularly in the determination of cirrhosis, but is less reliable in obese individuals. Thus, it is recommended to combine serum markers and elastography to maintain testing accuracy.36 There are other more accurate imaging methods for fibrosis e.g. MR elastography, but these techniques are expensive and not widely available.[37]

Table 5 Serum biomarkers and cut-off values for prediction of hepatic steatosis and significant fibrosis

Test/score	Cut off values	Sensitivity (%)	Specificity (%)
FLI – Fatty liver index	> 60	61	86
HSI – Hepatic steatosis index	> 36	45	93
NFS – NAFLD fibrosis score[a]	≥0.676	43	96
ELF – Enhanced liver fibrosis	>0.3576	80	90
FIB-4 indexb	≥2.67	33	98
Fibro-Test®	>0.30	92	71

Formula:
[a] NAFLD fibrosis score = −1.675 + 0.037 − age (years) + 0.094 − BMI (kg/m^2) + 1.13 × [Impaired fasting blood glucose/diabetes mellitus (yes = 1, no = 0)] + 0.99 × AST/ALT ratio − 0.013 × platelet count (×109/l) − 0.66 × albumin (g/dl)
[b] FIB-4 index =Age (years)×AST (U/L)/[PLT(109/L)×ALT1/2 (U/L)]

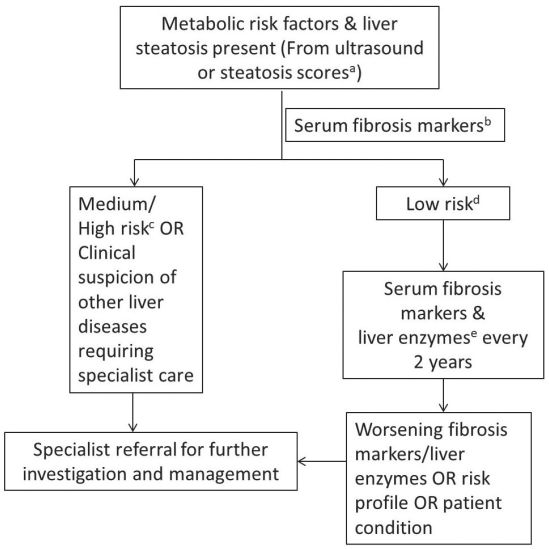
Based on the discussion so far we have suggested a practical approach which may be utilised by generalists to assess and monitor patients with suspected NAFLD (Figure 1). Where diagnostic or therapeutic uncertainties exist, liaison with hepatologists should be considered.

How to manage fatty liver?

Non-pharmacological management is the key intervention

Central to the strategy of management is weight loss by means of dietary and lifestyle modifications. Underlying metabolic disorders such as cardiovascular diseases, type 2 diabetes mellitus, insulin resistance, hypertension and dyslipidaemia will also benefit from weight loss. In overweight or obese patients, achieving 7–10% weight loss over one year has been shown to improve liver enzymes and histology.[38] Calorie restrictive diet with a daily negative calorie balance of 500–1000 kCal, targeting a weekly weight loss of 0.5–1kg has been shown to reduce hepatic steatosis.[39] Modified alternate-day calorie restriction (MACR) for eight weeks, a form of intermittent fasting, could improve both hepatic steatosis and fibrosis with good patient adherence.[40]

Figure 1 Suggested algorithm to assess and monitor suspected NAFLD patients for non-hepatologists.



[a] Steatosis scores: FLI, HSI (Table 4)
[b] Serum fibrosis markers: NFS, FIB-4, Fibro-Test® , ELF (Table 4)
[c] Medium/high risk: significant fibrosis or cirrhosis (F≥2) (Table 3, Table 4)
[d] Low risk: no/mild fibrosis (F0-F1) (Table 3, Table 4)
[e] Liver enzymes: aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT)

Structured aerobic exercise and resistance-training exercise regimes consisting of 150 to 200 minutes of moderate-intensity physical activity (e.g. stationary cycling or brisk walking) divided into three to five sessions weekly has been shown to be moderately beneficial in reducing hepatic steatosis.[2,41] Physical activity and dietary modifications complement each other in achieving weight loss. Other recommendations such as a Mediterranean diet,[42] avoidance of fructose,[43] reduction of alcohol consumption below the risk threshold (<30 g/day for men and <20 g/day for women) with complete alcohol abstinence in patients with cirrhosis[2,44] have shown promising results. Consumption of regular filtered coffee without sugar or milk was found to be protective for liver fibrosis. However, espresso consumption was not found to be beneficial.[45,46]

Does pharmacotherapy play any role?

Only patients with histologically confirmed NASH should receive pharmacotherapy, with stronger indications for patients with significant fibrosis (≥F2). Unfortunately, the Food and Drug Administration (FDA) has not approved any drugs for NASH. Therefore any pharmacotherapy would be considered currently as prescribed off-label.[2] Among the investigated medications, pioglitazone, vitamin E, liraglutide and obeticholic acid have been the more promising at present (Table 6).[47–49] However, there are a number of ongoing clinical trials involving cenicriviroc, elafibranor, obeticholic acid, liraglutide, and semaglutide which could potentially expand treatment options.[50] At the time of writing, obeticholic acid is awaiting FDA review for NAFLD patients. The dual peroxisome proliferator-activated receptor (PPAR) agonist, saroglitazar has shown positive results in an ongoing Phase II trial.[51] Unfortunately the first-line antidiabetic medication, metformin was not shown to reduce liver steatosis.[52]

With individualised treatment, these medications are useful for the management of the underlying metabolic diseases. Prescribing GLP-1 agonists for type 2 diabetes mellitus would be beneficial for its weight loss effect, while pioglitazone would be beneficial in selected NAFLD patients with type 2 diabetes where weight gain is not a concern. To address cardiovascular risk, statins can be used to treat dyslipidaemia based on various guideline-recommended targets. Statin use in NAFLD is safe, and may even significantly reduce aminotransferase levels with no additional hepatotoxicity risk.[2,53]

Role of bariatric surgery

In patients where lifestyle changes and pharmacotherapy fail, bariatric surgery can be considered to achieve weight loss targets and reduce metabolic syndrome complications. Bariatric surgery has been shown to reduce hepatic steatosis, necroinflammation and fibrosis in selected patients.[54] Procedures such as Roux-en-Y gastric bypass, duodenal switch, laparoscopic adjustable gastric banding and laparoscopic sleeve gastrectomy were found to be effective in inducing weight loss. Patients with BMI of ≥40 kg/m^2 or a BMI of ≥35 kg/m^2 with comorbidities such as diabetes mellitus or hypertension are indicated for bariatric surgery, but not for those with liver disease due to NASH. Unfortunately,

Table 6 Randomized controlled trials (RCT) of pharmacological agents with liver histology improvement in NAFLD.

RCT	Results	Duration (weeks)	Additional notes
PIVENS trial NASH (Type 2 diabetes mellitus not included) Pioglitazone 30 mg OD vs Vitamin E 800 IU OD vs Placebo	Compared to placebo, vitamin E and pioglitazone improved hepatic steatosis and lobular inflammation but not fibrosis	96	Weight gain was a side effect of pioglitazone
LEAN programme Liraglutide 1.8 mg OD vs placebo	NASH resolution with liraglutide (39%) vs placebo (9%)	48 to 72	No significant improvement in hepatic fibrosis
FLINT trial Obeticholic acid 25 mg OD vs placebo	Hepatic steatosis, lobular inflammation, balloon degeneration and hepatic fibrosis were better with obeticholic acid (45%) vs placebo (21%)	72	Obeticholic acid caused increased LDL cholesterol and pruritus (23%)

for patients with liver cirrhosis, whether compensated or decompensated, the risk of postoperative mortality can be increased from 2 to 21-fold.[55] Recently, endoscopic bariatric procedures such as intragastric balloon and transpyloric shuttle may be recommended in patients unfit for surgery.[56]

The road ahead

Recently there has been a growing international consensus support for nomenclature to change from NAFLD to MAFLD.[1,11] This will perhaps lead us to a better understanding and refocus our efforts on metabolic disease that seems to be central in the pathophysiology of NAFLD. It is inevitable that other liver disease aetiologies coexist in patients with NAFLD due to high NAFLD prevalence. Echoing the success of chronic hepatitis C treatment in recent years, it would be hard to imagine treating non-A, non-B hepatitis with modern direct acting antiviral therapy if we did not find the cause and rename it as hepatitis C, or that its sub-genotypes would be genetically sequenced after discovery. In a similar fashion, perhaps it is the hope of experts that by renaming NAFLD as MAFLD, we would be able to subtype, individualise and discover novel pathways crucial to its ultimate treatment.

Conclusion

Our current understanding of NAFLD has greatly advanced in recent decades, from a condition of unknown aetiology in the 1980s to a disorder that is largely of metabolic origin in 2020. Complications include liver morbidities e.g. cirrhosis and HCC; most deaths are due to cardiovascular causes. Current non-invasive tests are similarly accurate, more accessible and safer than liver biopsy; however, there is a dire need for a diagnostic algorithm that is clearer for general physicians. Non-pharmacological lifestyle intervention is key, but to address fibrosis and NASH, pharmacotherapy is necessary and clinical trials are ongoing. In situations where diagnostic or therapeutic uncertainties exist, prompt referral to hepatologists is recommended. Lastly, a good step forward is to move towards a consensus to better define NAFLD as a metabolic disease.

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