

Diagnosis and management of fatty liver disease – An update

De Silva S. D. N¹, Wickramarachchi A.W¹, Premadasa B.A.M¹, Nimesha A.G.S¹, Katulanda P^{1,2}

¹ University Medical Unit, National Hospital of Sri Lanka, Colombo, Sri Lanka

² Department of Clinical Medicine, Faculty of Medicine, University of Colombo, Colombo, Sri Lanka

Correspondence email: neomalde@gmail.com

 <https://orcid.org/000-0003-3763-2020>

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is characterized by hepatic steatosis associated with insulin resistance in the absence of excessive alcohol consumption or any other competing etiology. There are two methods to define hepatic steatosis. The presence of steatosis in more than 5% of hepatocytes in the histological examination is the first method. The second method is the detection of more than 5.6% of fatty material in the liver (proton density fat fraction) assessed by proton magnetic resonance spectroscopy (HMRS) or quantitative fat/water selective magnetic resonance imaging (MRI). Non-alcoholic fatty liver (NAFL) is the presence of hepatic steatosis more than 5% without evidence of hepatocellular injury. Non-alcoholic steatohepatitis (NASH) can progress to fibrosis, cirrhosis and hepatocellular carcinoma (HCC) (1).

Pathophysiology

The liver is not a primary organ of fat storage, but, in patients with NAFLD, triglycerides accumulate in the liver. There are 3 main sources of this excess fat; uptake of non-esterified fatty acids (NEFA) from plasma, dietary fat and de-novo synthesis of lipid in the liver (2). Insulin resistance or the inability of the peripheral tissues to adequately respond to insulin is the main underlying factor of this process. Insulin usually inhibits lipolysis in the adipose tissue. In insulin resistance, lipolysis is increased and excess free fatty acids enter the plasma. Therefore, increased amounts of fatty acids enter the liver in a concentration-dependent manner. Insulin resistance also causes hyperglycaemia which along with hyperinsulinemia stimulates de-novo lipid synthesis in the liver (3). Gut microbiota and genetic factors

also contribute to the pathogenesis of NAFLD. Gut microbiota increases the delivery of endotoxins, microbiota metabolites and nutrients to the liver by increasing gut permeability. This leads to hepatic fat accumulation and inflammation(4). Patatin-like phospholipase domain-containing 3 (PNPLA3) gene variant which is a determinant of hepatic fat content is one major genetic factor that contributes to NAFLD (5). The transmembrane 6 superfamily member 2 (TM6SF2) E167K gene variant leads to reduced VLDL secretion from the liver which results in triglyceride accumulation in hepatocytes (6).

Epidemiology and NAFLD in lean individuals

NAFLD is the most common liver disorder in developed countries, affecting 17–46% of adults (1). The prevalence of NAFLD based on ultrasound scan findings among a sample of participants from an urban community in Sri Lanka was 32.6% (7). NAFLD is also present in 7% of normal-weight (lean) persons. Lean patients with NAFLD are younger, more likely to be female and had lower rates of insulin resistance, hypercholesterolemia, diabetes and hypertension compared with obese patients with NAFLD(8). Lean NAFLD is more common in Asians (9).

Risk factors and associations

Obesity, type II diabetes mellitus, dyslipidaemia, metabolic syndrome and polycystic ovary syndrome are commonly associated with NAFLD. Hypothyroidism, obstructive sleep apnea, hypopituitarism, hypogonadism, pancreatoduodenal resection and psoriasis are its other associations (10). Risk factors for NAFLD in lean patients include high body fat, body weight gain even within normal weight

limits, high fructose and high cholesterol intake, and genetic risk factors (9).

NAFLD or MAFLD?

The term Non-Alcoholic Fatty Liver Disease was coined to describe chronic liver cell disease in patients without a history of significant alcohol consumption and any other obvious etiology such as chronic hepatitis infection, autoimmune liver disease, Wilson's disease and hereditary haemochromatosis. Therefore, it was essentially a diagnosis of exclusion and is a heterogenous entity. However, liver disease associated with metabolic dysfunction has been identified as a distinct entity and the term Metabolic dysfunction-associated fatty liver disease (MAFLD) has been suggested instead of NAFLD. "Positive" diagnostic criteria have been proposed for this entity and therefore, it is no longer considered a diagnosis of exclusion (11). Furthermore, newer nomenclature appreciates the fact that MAFLD can co-exist with liver disease of other etiology such as alcohol and chronic hepatitis infection. A recent study conducted in Sri Lanka showed that the MAFLD definition was more useful in predicting future adverse outcomes than the NAFLD definition (12).

Natural history

Benign fatty liver has a very low risk of progressing to cirrhosis. However, necroinflammation in initial biopsy is the most significant predictor of progression to advanced fibrosis. Other predictors of progression to advanced fibrosis include age (over 50 years), BMI over 28 kg/m², hypertension, insulin resistance/ diabetes mellitus and abnormal aminotransferases (13). Those with NAFLD have significantly higher overall and liver-related mortality rates compared to the general population and cardiovascular disease was the leading cause of death further emphasizing the fact that NAFLD or MAFLD is the hepatic manifestation of the multi-system disease of metabolic dysfunction (14).

Clinical features

Most patients with NAFLD or MAFLD are asymptomatic. But some may complain of non specific symptoms such as fatigue, malaise and vague right upper abdominal discomfort. The prevalence of hepatomegaly among patients with NAFLD may vary between 5% to 18% depending on the setting and the population studied (15).

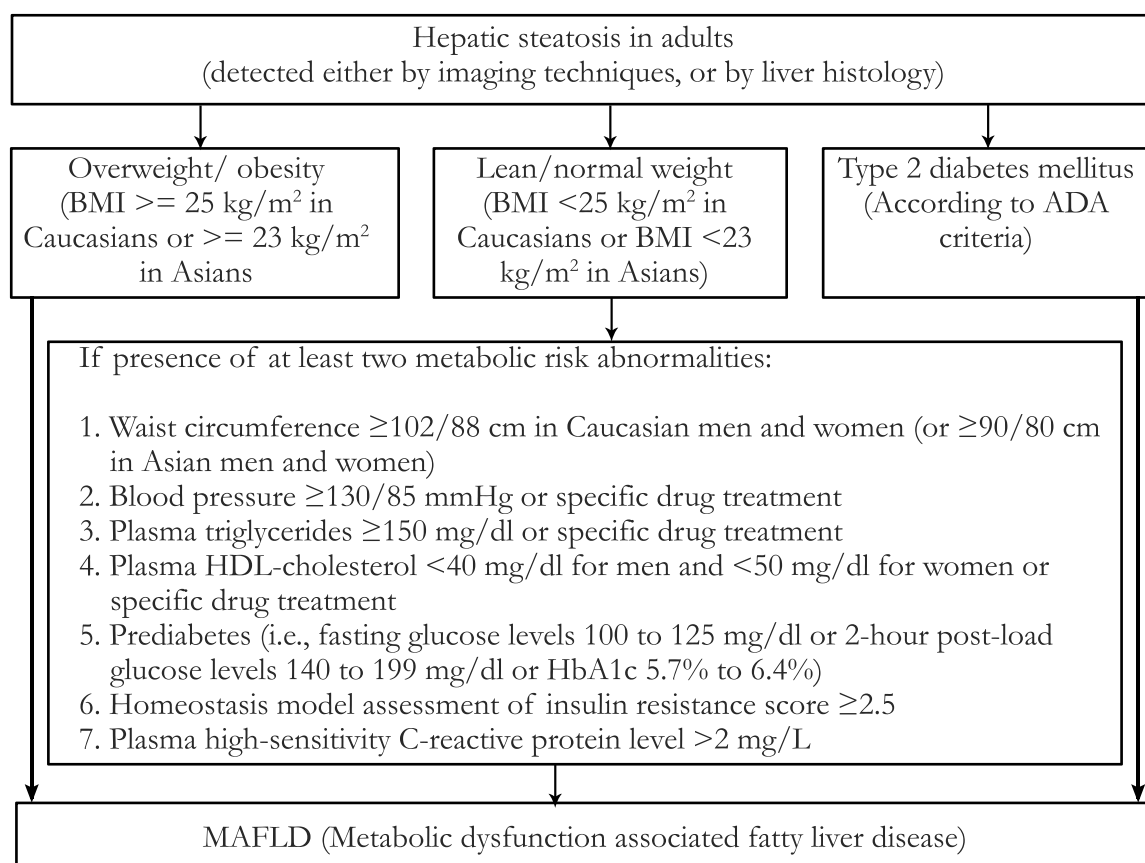


Figure 1: Proposed diagnostic criteria for MAFLD (BMI – body mass index, ADA – American diabetes association, HDL – high density lipoprotein)

Diagnosis

Above criteria have been proposed (Figure 1) for the diagnosis of MAFLD (11).

Evaluation of a patient with MAFLD

Clinical prediction tools like NFS (NAFLD Fibrosis Score which is based on age, BMI, hyperglycaemia, platelet count, albumin and AST/ALT ratio) and FIB-4 index (based on platelet count, age, AST and ALT) are better than indices such as BARD (based on AST/ALT ratio, BMI and diabetes), APRI (based on AST and platelet count) and AST/ALT ratio and as good as MR elastography in predicting advanced

fibrosis (16). Enhanced liver fibrosis (ELF) panel which is a combination of 9 serum markers of liver fibrosis showed 90% sensitivity in detecting fibrosis (17).

A liver biopsy should be considered;

- 1) In patients with high risk of steatohepatitis and/or advanced fibrosis
 - 2) When presence of other etiologies for liver disease can't be excluded without a biopsy
- Imaging studies help to detect hepatic steatosis and quantify it and to detect advanced fibrosis to help staging and prognostication of NAFLD.

Table 1: Imaging modalities used in diagnosis and staging of NAFLD

Imaging	Comments
Ultra sound scan	Widely available first line investigation. Sensitivity and specificity high when hepatic steatosis >20%
CT without contrast	Useful in morbidly obese.
Vibration-controlled transient elastography – FibroScan	Can be point of care. Most reliable in ruling out advanced hepatic fibrosis (great NPV)
MR elastography/ MR spectroscopy/ LiverMultiScan	Requires radiology referral Most accurate of the imaging modalities
2D shear wave elastography	May require radiology referral but can be point of care with minimal training

Management of MAFLD

Management of MAFLD consists of

- Lifestyle modification and weight reduction
- Management of other metabolic risk factors
- Liver directed pharmacotherapy

Diet and lifestyle modifications

Lifestyle modification is the mainstay of the management of the non-alcoholic fatty liver disease. The degree of weight loss positively correlates with the reversibility of damage caused by NAFLD. A 3% weight loss is associated with reversibility of steatosis and seven to ten percent of weight loss can reverse steatohepatitis. More than 10% weight loss can improve the fibrosis stage. A recent study (n=293) showed an improvement in liver steatohepatitis in 58% of those achieving >5% and

in 90% of those achieving >10% weight loss respectively; only the latter demonstrated an improvement in the fibrosis stage (in 45%) (18). Similarly, studies in Asian populations support the dose-response effect of weight loss with a 7–10% weight loss target; whereas about 40% of those with MAFLD have some improvement even with 3–5% weight reduction.

The setting of individualized goals plays an important role in order to achieve targets of lifestyle modification. These goals should be specific, measurable, achievable, relevant, and timely. (known as SMART). A hypocaloric diet with an energy deficit of 500-1000 kcal, to induce a weight loss of 500-1000 g weekly is recommended. MAFLD is associated with unhealthy dietary habits containing processed food and beverages with refined sugar, saturated fatty acids and low content of omega 3, 6 fatty acids, fibre, polyphenols and micronutrients (19). Mediterranean

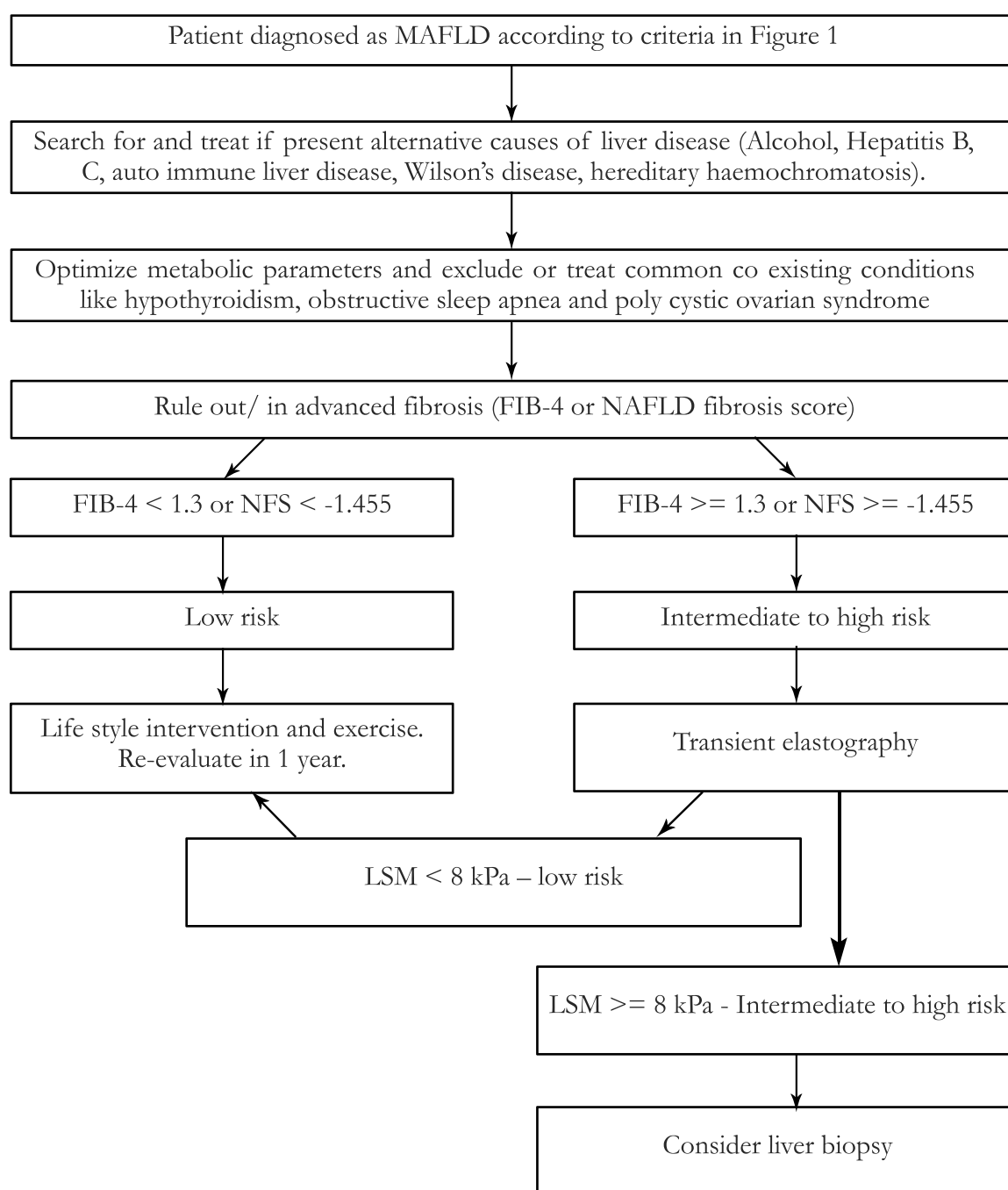


Figure 2 : Evaluation of a patient with MAFLD (MAFLD – metabolic dysfunction associated fatty liver disease, FIB-4 – fibrosis- 4 index based on platelet count, age, AST and ALT, NFS – non-alcoholic fatty liver disease fibrosis score based on age, body mass index, hyperglycaemia, platelet count, albumin and AST/ALT ratio, LSM – liver stiffness measurement)

diet may be beneficial in NAFLD since, it is more enriched in polyphenols, omega 3 fatty acids, with low-carbohydrate content.

Meta-analysis of observational studies (n = 7) and RCTs (n = 6) of liver steatosis and cardiometabolic risk factors in patients with NAFLD following a Mediterranean diet revealed that Mediterranean diet is associated with a significant improvement in hepatic steatosis

Examined by magnetic resonance spectroscopy (MRS), but not by ultrasound. Mediterranean diet was also associated with a reduction in BMI, triglycerides, homeostatic model assessment of insulin resistance (HOMA-IR) and was inversely associated with NAFLD (20). Recently conducted, DIRECT PLUS is a randomized, open-label trial in patients with abdominal obesity/dyslipidemia following 18 months of healthy dietary guidelines, Mediterranean diet, or green-Mediterranean diet (N = 294), showed that the

latter group was associated with loss of intrahepatic fat. Green Mediterranean diet is a calorie-restricted diet rich in vegetables, replacing red meat with poultry and fish (21). Meta-analysis of 10 international clinical trials of low-carbohydrate (<50%) diets in patients with NAFLD showed that it was associated with a significant reduction in intrahepatic lipid content without significant reductions in serum transaminases. A systematic review and meta-analysis showed a significantly decreased risk of MAFLD and liver fibrosis among regular coffee drinkers. The recommended amount is black coffee two to three cups without added sugar (22).

Sustaining achieved weight loss is crucial in order to get the maximum benefit. A Multidisciplinary approach should be applied to encourage maintenance of lifestyle modification.

Exercise

At least 30 minutes per day of moderate-intensity exercise for a minimum of 5 days per week or at least 20 minutes of vigorous exercise for a minimum of 3 days per week is recommended for the general population. Resistance exercises on 2–3 days/week and flexibility exercises >2 days/week are also recommended (22). Moderate to vigorous-intensity exercise showed benefits in preventing the onset of fatty liver and in the resolution of existing fatty liver (23). A systematic review suggested that both aerobic and resistance exercise reduces hepatic steatosis equally in MAFLD, while resistance exercise does this with less energy consumption. Therefore, resistance exercise is found to be a better-tolerated exercise for MAFLD patients with poor fitness or for those who cannot tolerate or participate in aerobic exercise (24). The type and intensity of exercise have to be individualized in order to achieve the target weight.

Bariatric surgery for NAFLD

The prevalence of NAFLD and NASH among obese is found to be 50-90% and 10-50% respectively compared to the prevalence in the general population which is 10-30% and 3-5% for NAFLD and NASH respectively (25). Though lifestyle modification and weight reduction through diet and exercise have been shown to improve the progression of NAFLD the long-term adherence to diet and exercise is limited. Bariatric surgery including Roux en Y bypass (RYGB) and sleeve gastrectomy (SG) procedure has shown improvement in steatosis, hepatitis, ballooning, or fibrosis in obese patients even with significant

pre-procedure histology at baseline (26,27). A meta-analysis has demonstrated improvement in histopathology of NAFLD in more than 75% of patients and complete resolution of steatosis in the majority (27). Also, a case-control study of 2942 biopsy-proven NAFLD patients who underwent bariatric surgery was found to have a reduced risk of progression to cirrhosis compared to controls (28).

However, data regarding bariatric surgery is not conclusive and randomized control studies are lacking. A systematic review that found no randomized control trial and was carried out among 21 retrospective and prospective cohort studies also confirmed improvement in steatosis and inflammation but 4 trials noted worsening of fibrosis following surgery (29). Also, there was significant bias and underreporting of adverse effects.

Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy (SG) adjustable gastric band (AGB) and biliopancreatic diversion (BPD) all appear to benefit the majority of patients with NAFLD. A meta-analysis of different bariatric procedures showed a pooled outcome of improvement of steatosis in 88%, steatohepatitis in 59% and fibrosis in 30%. RYGB showed improvement above the average of pooled analysis (30).

Due to the inconsistencies in the evidence, NAFLD is not a sole indication for bariatric surgery. If bariatric surgery is performed in a patient with suspected NAFLD, taking a needle biopsy is advised during the surgery and monitoring of liver transaminases is advised to identify the patients who develop worsening of fibrosis.

Pharmacological treatment

In patients without diabetes

PIVENS trial conducted among biopsy-proven NAFLD patients without diabetes in 2010 showed significant lowering of hepatic aminotransferases and hepatic steatosis, lobular inflammation and NAFLD activity score with Vitamin E at a dose of 800IU daily and Pioglitazone at a dose of 30mg daily. But fibrosis was not improved with either of these treatments and steatohepatitis was reduced only with Pioglitazone (31).

Subsequent meta-analysis has shown not only improvement of serum transaminases but improvement of liver histology including steatohepatitis and fibrosis with the use of Vitamin E (32). In addition, vitamin E therapy has been shown

to improve transplant-free survival and the rate of decompensation among patients with established bridging fibrosis (33). However, the SELECT study has shown an increase in the incidence of prostate cancer among long term vitamin E users (34). Since the studies showed benefit with Vitamin E enrolled patients without diabetes its use in patients with diabetes is not recommended. Thus, Vitamin E should be reserved for patients without diabetes with biopsy-proven NASH.

In patients with diabetes

Similarly, pioglitazone has also been shown to improve liver histology including balloon degeneration, steatohepatitis and fibrosis in a meta-analysis (35,36). Therapy with pioglitazone was associated with peripheral oedema, weight gain without significant change in body fat composition and reduction in bone mineral density (36,37). There was no change in HOMA-IR score with pioglitazone use (37). Though the initial animal studies and a clinical trial has shown an increased risk of bladder cancer with pioglitazone use (38) this was subsequently not proved in the meta-analysis (39). Therefore, Pioglitazone is recommended in patients with or without diabetes with biopsy-proven NASH and due to the safety concerns should not be used without biopsy-proven NASH.

Metformin

Meta-analyses have shown that though Metformin use improves transaminase levels and HOMA-IR score in patients with NAFLD, it does not improve liver histology (40,41).

Newer hypoglycaemic drugs in the management of NAFLD

GLP1 receptor agonists

Diabetes and obesity are the main risk factors associated with NAFLD. Also, weight loss has been positively associated with the reversal of histological effects of NASH. Thus, it is natural to assume newer antidiabetic drugs such as SGLT2 inhibitors and GLP1 receptor agonists to be effective in treating NAFLD.

Weekly 1.8mg of liraglutide was studied in a randomized control trial in obese patients with clinical evidence of NASH, and an end of treatment biopsy was obtained which showed less likelihood of fibrosis progression and higher steatosis resolution in the treatment group (42).

Semaglutide has been shown to significantly improve glycaemic control as well as cardiovascular outcomes in the SUSTAIN series of trials among patients with diabetes (43). Its effect on weight reduction among non-diabetics was confirmed in a recent randomized control trial which showed a mean 14.9% weight reduction compared to 2.4% in placebo at 68 weeks with a weekly semaglutide dose of 2.4mg (44).

A recent randomized control trial among biopsy-proven NASH and liver fibrosis stage F1-F3 showed that NASH resolution was achieved among 59% of patients treated with Semaglutide at a dose of 0.4mg compared to 17% in the placebo group. Though lower doses also showed significant improvement compared to placebo they were less effective. Though there was a numerically higher number of patients with improvement of fibrosis stage in Semaglutide treated group this finding was not significant statistically. The mean weight loss achieved was 14% in the semaglutide treated group (45). There were more gastrointestinal side effects, primarily nausea reported in the treatment group. Further studies on higher doses of Semaglutide and additional data on histological outcome is needed for routine use of this drug in the clinical setting in the absence of other indications.

SGLT2 inhibitors

The effect of empagliflozin in liver fat was studied via MRI derived proton density fat fraction in an E-LIFT study among 50 diabetic patients with NASH (46). Empagliflozin was associated with a significant reduction of liver fat content and ALT levels compared to placebo. Small scale studies done to evaluate the effects of SGLT2 inhibitors on the histological parameters of NASH has shown a reduction in steatohepatitis, ballooning and fibrosis (47). These effects have to be confirmed in large scale clinical trials before these drugs can be prescribed routinely in the absence of other indications. The effect of SGLT2 inhibitors on NASH in non-diabetics also need further evaluation.

Cardiovascular risk reduction in MAFLD

Cardiovascular disease is the commonest cause of death in MAFLD (48). In patients with metabolic syndrome, fatty liver is an independent predictor of carotid atherosclerosis (49). Therefore, management of MAFLD should focus not only on slowing the progression of liver disease but also on cardiovascular risk reduction. A post hoc analysis of the GREECE study (Greek Atorvastatin and Coronary Heart Disease Evaluation) showed that statin therapy can

improve liver function tests and reduce cardiovascular events (50). A post hoc analysis of the IDEAL study showed that the cardiovascular risk reduction benefit of high-intensity statin therapy was greater in patients with mild to moderately elevated ALT at baseline than those with normal ALT at baseline (51). Therefore, in patients at high risk of cardiovascular disease moderately elevated liver function tests should not be a barrier to even high-intensity statin therapy.

Patients with NAFLD have a higher risk of developing new-onset hypertension and vice versa. Proposed pathophysiological mechanisms for this bi-directional relationship include insulin resistance, activation of renin-angiotensin-aldosterone system and sympathetic nervous system, and arterial stiffness. Proper blood pressure control may result in attenuation of progression to liver fibrosis. Multiple small studies have shown the benefit of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in attenuation of progression or amelioration of liver fibrosis (52). However large randomized controlled trials are needed to confirm these findings.

Summary

Diagnostic criteria have been proposed for the diagnosis of MAFLD thus making it a better defined entity. Scoring systems, non-invasive imaging and serum markers help to identify patients who may need a liver biopsy and liver-directed pharmacotherapy. While dietary modifications, lifestyle interventions and exercise remain the cornerstone of therapy pharmacotherapy of MAFLD remains an area of uncertainty and research interest. Mitigating the cardiovascular disease risk with optimal control of metabolic risk factors plays a pivotal role in the management of MAFLD.

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