Introduction

This clinical practice guideline on the evaluation and treatment of non-alcoholic fatty liver disease (NAFLD) among adults is a product of a joint effort by The Sri Lanka College of Endocrinologists (SLCE) and Sri Lanka Society of Gastroenterology (SLSG). This guideline is based on extensive, up to date evidence search made by the guideline team and selected to match the clinical context and available resources. The ultimate purpose of the guideline is to increase awareness and to improve patient care of non-alcoholic fatty liver disease (NAFLD), and to assist caring physicians in the decision-making process by providing
evidence-based guidance considering the health care burden posed by the management of the disease.

Definitions

NAFLD is defined as the presence of hepatic steatosis (HS) (fatty liver, >5% fat in the liver), in the absence of any secondary cause for HS. Exclusion of ‘unsafe’ alcohol consumption above Asian standards (>14 units per week for males and >7 units per week for females) is essential for the diagnosis. In appropriate situations, other causes of HS such as chronic viral hepatitis, autoimmune and hereditary liver disease, and contribution of steatogenic drugs should be also excluded.\(^1\)

HS is most commonly established by liver ultrasonography. Less commonly, other imaging modalities such as CT or MRI scanning will be required to establish HS. Liver biopsy and histology is rarely required for the diagnosis. NAFLD is a spectrum of disorders ranging from simple steatosis [non-alcoholic fatty liver (NALF)], non-alcoholic steatohepatitis (NASH) and NASH-related cirrhosis.

Incidence and Prevalence of NAFLD

The incidence and the prevalence of the NAFLD have risen exponentially in the recent past (Figure 1). In Sri Lanka, the prevalence of ultrasonically detected NAFLD among urban adults is 32.6% (6) and among rural adults is 18% (7). The annual incidence of NAFLD among urban adults is 6.6% (8).

### Table 1. Definitions of NAFLD

| Definition                                                                 | Description                                                                 |
|---------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| NAFLD (Non-alcoholic fatty liver disease)                                 | There should be evidence of hepatic steatosis (HS), either by imaging or histology and absence of secondary causes of hepatic fat accumulation such as significant alcohol consumption, long term use of a steatogenic medication, hereditary and autoimmune liver disorders.\(^2\) |
| NAFL (Non-alcoholic fatty liver)                                          | The presence of HS without evidence of hepatocellular injury (hepatocyte ballooning) |
| NASH (non-alcoholic steatohepatitis)                                      | The presence of HS and inflammation with hepatocyte injury (ballooning), with fibrosis (F1-4) or without (FD) fibrosis |
| Lean NAFLD                                                                | NAFLD that develops in patients with a body mass index (BMI) <23 kg/m²(3,4) |
| NASH cirrhosis                                                            | The presence of cirrhosis with current or previous histological evidence of steatosis or steatohepatitis |

Note: Fibrosis Severity Scale: F0 - No fibrosis, F1 - Mild fibrosis, F2 - Moderate fibrosis, F3 - Severe fibrosis, F4 - Cirrhosis
Pathogenesis and pathophysiology

Fatty liver is considered to be the hepatic component of metabolic syndrome. Although the pathogenesis of NAFLD/ NASH is not yet fully understood, several theories are currently available to describe its development. Steatosis represents the ‘first hit’, which then sensitizes the liver to injury mediated by ‘second hits’, such as inflammatory cytokines, adipokines, oxidative stress, angiotensinogen, norepinephrine, osteopontin and mitochondrial dysfunction, leading to steatohepatitis and fibrosis. Furthermore, accumulation of FFA alone has been suggested to be sufficient to induce liver damage, without recourse for a second hit. Oxidative stress reduces the ability of mature hepatocytes to proliferate leading to increased hepatocyte death (9). Additionally, several agents including leptin, insulin, glucagon, deacylated ghrelin, selenoprotein P levels are increased while levels of adiponectin, GLP 1, acylated ghrelin are decreased in NAFLD contributing to the pathophysiology of the disease as described in (figure 2) (10).

There seems to be a genetic predisposition (11) to the development of NALFD. Some of the established association of genetic variants for development and progression of fibrosis in NAFLD include PNPLA3 (patatin-like phospholipase domain-containing protein 3), TM6SF2 (trans-membrane-6 super-family-2) and MBOAT7 (membrane bound O-acetyltransferase domain containing 7). Out of these variants PNPLA3 (12) has been proven to be associated with NAFLD in Sri Lanka.

Recently there is accumulating data that the gut microbiome may play a key role in the development and progression of NAFLD via lipopolysaccharides, inflammatory cytokines and bile acid derivatives (12).
Risk factors and modifiers
- Dietary fat
- Genetic predisposition
- Gut microbiome

Increased visceral adipose tissue

Proinflammatory mediators

Insulin resistance

Increased FFA

Liver

Altered glucose metabolism

Altered lipid metabolism

Hepatic steatosis

Steatohepatitis

Hepatocyte injury ( ballooning)

Endoplasmic reticulum stress

Lipotoxicity

Inflammation

Portal endotoxin

Intestinal dysbiosis

Mitochondrial dysfunction

Oxidative stress

Hepatocyte death

- Necrosis
- Necroptosis
- Apoptosis

- Activation of hepatic stellate cells

- Collagen deposition

Fibrosis

Cirrhosis

Hepatocellular cancer

Figure 2: Pathophysiology of the development of NAFLD

Figure 2: Pathophysiology of the development of NAFLD
NAFLD is strongly associated with metabolic syndrome as well as its individual components.

**Obesity**

Obesity carries a 3.5 fold increased risk of developing NAFLD (13). Prevalence of NAFLD among obese individuals is 70%. Further, obese NAFLD, when compared to non-obese NAFLD has a higher transaminases, higher degree of hepatic steatosis and increased risk of liver fibrosis, hypertension, diabetes mellitus, and metabolic syndrome (14). However, some individuals with NALFD will have normal BMI (<23kg/m²). They are referred to as lean NALFD and accounts for up to 12% of NALFD in Sri Lanka (15).

**Type 2 diabetes mellitus**

The overall prevalence of NAFLD among T2DM is 70 % (16). 2-5 times increased risk of incidental T2DM is demonstrated in NAFLD and its incidence reduces with resolution of fatty liver (17). However, T2DM and NAFLD can develop almost simultaneously in a patient due to the common risk factors for both conditions, confounding the prevalence of NAFLD in patients with T2 DM or vice versa.

**Dyslipidemia**

Nearly half of the patients with dyslipidemia were found to have NAFLD, with higher prevalence in those with high triglycerides and low HDL levels. (High TG: HDL ratio and/or high Total cholesterol/HDL ratio) (18).

**Malignancies**

NAFLD increases the risk of hepatocellular carcinoma by 10 times. The presence of NAFLD doubles the risk of colon cancers in men and breast cancers in women (19).

**Other associations**

NAFLD increase the risk IHD by 1.5 times and chronic kidney disease by 2 times (20). Polycystic ovarian syndrome and hypothyroidism are other known associations of NAFLD.

**Death**

The leading cause of mortality among patients with NAFLD is cardiovascular disease. This is followed by cancer-related deaths and liver-related deaths. These deaths are strongly associated with the presence of significant or advanced liver fibrosis (>F2 – bridging fibrosis or cirrhosis) rather than the presence of NAFL/NASH alone (21).

**Natural history and outcomes**

The progression of NAFLD ranges from simple steatosis to hepatic inflammation, subsequent fibrosis with development of cirrhosis, and hepatocellular carcinoma (HCC). The time for progression from one stage to another varies according to the underlying disease stage. Natural history of the NAFLD is summarized in Figure 3.
Cardiovascular disease is the leading cause of mortality in NAFLD(21). This is followed by cancer-related deaths due to extra-hepatic malignancies such as colorectal cancer in males and breast cancer in females as the second common cause of death in NAFLD. Liver-related deaths are only the third most common cause of death in NAFLD(22). This highlights the importance of screening and treating associated cardiovascular risk factors and screening for appropriate malignancies among patients with NAFLD.

Patients with NASH have six-time higher mortality compared to those with isolated NAFL(23, 24). Similarly, patients with NASH and significant liver fibrosis have worse outcomes compared to those without significant liver fibrosis. Presence of significant liver fibrosis will increase all cause, cardiovascular and liver related mortality in NAFLD(25-27).

**Screening**

Screening for NAFLD can be recommended in ‘high risk’ patients such as obese and those with type 2 diabetes, dyslipidemia and metabolic syndrome, due to their strong association. Persons with persistently abnormal liver enzymes also should be screened for NAFLD (28). Some lean individuals are also prone to get NAFLD (lean NAFLD). Therefore, vigilant screening of lean individuals with other features of metabolic syndrome should be practiced(29). Routine population screening or family screening is not recommended due to lack of evidence of benefit(30).

Ultrasound abdomen is recommended as an initial investigation for screening of NAFLD as it is non-invasive, easy to perform, cheap and readily available (28,31).

**Evaluation**

Evaluation of NAFLD includes diagnosis and staging of the liver disease and assessment of risk factors and associated diseases.

The diagnosis of NAFLD requires the evidence of HS on imaging or histology in the absence of other causes of steatosis or liver disease (30). Initial evaluation should include detailed medical, medication and family history to evaluate for risk factors, alternative etiology for liver disease and complications. Details of daily activity, physical exercise, dietary habits, alcohol and smoking habits, medical co-morbidities and current medications should be established.

General physical examination including weight, BMI to assess general obesity (23-24.9Kg/m² – over-weight, >25kg/m² – obesity), waist circumference to assess central obesity (>90cm in males, >80cm in females)(32), blood pressure, features of insulin resistance, findings suggestive of other etiologies of liver disease should be documented (Table 2) (28,30,33). Fasting blood sugar or HbA1c and fasting lipid profile should be performed routinely to identify those with associated diabetes and dyslipidemia.

| Table 2: Common causes for hepatic steatosis and liver disease |
|---------------------------------------------------------------|
| **Secondary causes of hepatic steatosis**                     |
| • "Unsafe" alcohol consumption                                |
| • Steatogenic medications - (corticosteroids, amiodarone, methotrexate, tamoxifen, valproate, antiretroviral) |
| • Chronic hepatitis C infection                               |
| • Parenteral nutrition                                        |
| • Severe malnutrition                                         |
| • Pregnancy associated liver disease                         |
| • Abetalipoproteinemia                                        |
| **Alternative causes of liver disease**                       |
| • Alcohol                                                    |
| • Hepatitis B/C infections                                    |
| • Hemochromatosis                                            |
| • Wilson disease                                             |
| • Autoimmune liver diseases                                  |
| • Drugs                                                      |
| • Alternative medicines                                      |
| • Alpha-1 antitrypsin deficiency                              |
Risk stratification to determine the stage of NAFLD will help to predict the progression of the disease, prognosis and identify the treatment candidates. This should be initially undertaken non-invasively with locally available tests (Table 3). High risk patients may be subjected to further evaluation including liver biopsy (28, 30, and 33).

Table 3. Non – Invasive Investigations for the evaluation of NAFLD

| INVESTIGATION                                | STRENGTHS                                                                 | LIMITATIONS                                                                 |
|----------------------------------------------|---------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Liver profile                                | • Mildly raised transaminases (ALT > AST) and Gamma glutamyl transferase  | • ALT values do not correlate with histological findings and severity     |
| Ultrasound abdomen                           | • Widely available and cheaper                                            | • ALT can be normal in >50% of individuals with NASH and 80% of individuals with NAFLD |
|                                              | • Additional assessment of hepato-biliary system                           | • Cannot distinguish between the stages of NAFLD.                         |
|                                              | • Sensitivity- 53-100%                                                    | • Suboptimal sensitivity and specificity for mild steatosis (<30%)        |
|                                              | Specificity- 77-98%                                                      | • Not reliable in obese individuals                                      |
| MRI                                          | Liver MRI scan                                                            | • High cost                                                               |
|                                              | • Gold standard among currently available tools                           | • Needs expertise                                                         |
|                                              | MR Spectroscopy                                                          | • Not widely available                                                    |
|                                              | • Quantitative estimation of liver steatosis                               |                                                                            |
|                                              | • Useful in research setting but not in clinical practice                |                                                                            |
|                                              | • Sensitivity- 77% to 100%                                               |                                                                            |
|                                              | Specificity- 87% to 91%                                                  |                                                                            |
| Fibro scan (controlled transient elastography (VCTE)) | • The most accurate imaging method to identify varying degrees of fat infiltration and fibrosis | • Suboptimal sensitivity and specificity for mild fibrosis                |
|                                              | • Sensitivity- 75% to 88%                                                | • Learning curve for technique                                            |
|                                              | Specificity- 85% to 90%                                                  | • Unreliable results in the presence of high BMI and thoracic fold thickness |
| Serum based scores                           | • Point of care tool                                                     |                                                                            |
| (NAFLD Fibrosis score (NFS) and FIB-4 index)  | • Can rule in/rule out advanced fibrosis                                 |                                                                            |
|                                              | • Sensitivity- 95%                                                       |                                                                            |
|                                              | Specificity – 77%                                                       |                                                                            |
|                                              | • Calculators are freely available in web                                | • Not validated in Sri Lankan population                                 |
|                                              | • The negative predictive values for excluding advanced fibrosis are higher, therefore, can exclude advanced fibrosis |                                                                            |

Note: FIB-4 comprises age, platelets and AST/ALT; NFS includes age, BMI, DM, platelets, AST/ALT, albumin. Based on the non-invasive assessment patients should be categorized to ‘Low risk of fibrosis or ‘High risk of fibrosis. Low risk of fibrosis – FibroScan (TE)<5 kPa, FIB-4 < 1.3, NFS < -1.455. High risk of fibrosis – FibroScan (TE)> 10 kPa, FIB-4 > 3.25, NFS > 0.676
Liver biopsy

Liver biopsy is the only method to reliably diagnose NASH and is the only investigation that reliably differentiates the stages of NAFLD. However it is invasive, expensive, requires expertise for interpretation and carries some morbidity and rarely mortality related to the procedure (28,30,33,34).

Liver biopsy may be considered in NAFLD/NASH in the following settings: 1. To exclude competing or coexisting etiologies for liver disease 2. Advanced fibrosis which is suggested by serum based scores and/or imaging 3. To establish the diagnosis of NASH in patients with poor response to therapy

Histology

Clinically useful pathology report should distinguish between simple steatosis and steatohepatitis. NAFLD encompasses: steatosis alone, steatosis with lobular or portal inflammation without ballooning or steatosis with ballooning but without inflammation. The diagnosis of NASH requires the joint presence of steatosis, ballooning and lobular inflammation. A comment on severity based on specific scoring systems such as NAFLD activity score (NAS) is useful. The presence of fibrosis should be described, and if present, a further statement related to location, amount and parenchymal remodeling is warranted (28, 30, 33, and 34).

Management strategies Management of NAFLD should ideally be via a multidisciplinary approach (30). This will increase the rate of diagnosis, improve metabolic measures and hepatic/ non-hepatic outcomes and reduce severity, which will be cost effective. This multi-disciplinary team will include Gastroenterologists/ Hepatologists, Endocrinologists, Cardiologists, Bariatric Surgeons, Nutritionists, Behavioral experts and specialist nurses. Whenever possible, patients should be managed by such Multidisciplinary team (MDT).

A successful management strategy should be tailor-made to the stage of the disease in the spectrum of NAFLD and may include following key components:

1. Non-Pharmacological treatment
   1.1 Achieving target weight loss
   1.2 Regular physical exercise
   1.3 Healthy dietary modifications

2 Pharmacological treatment

3 Management of risk factors and metabolic associations
Algorithm 1: Evaluation of NAFLD

- **SUSPECTED NAFLD**
  - Hepatic steatosis on imaging with elevated serum ALT
  - Evaluate alcohol consumption
  - Confirmation of NAFLD
  - Evaluate alternative causes of High ALT

2 step diagnostic strategy for NAFLD

1st Step:
- Clinical biomarkers, scoring systems (FIB-4, NFS)
- Selection of patients who require further inspection of liver fibrosis
- Ultrasound based elastography, MR elastography

Non-invasive risk stratification

Low risk profile:
- BMI < 29.9 kg/m²
- Age < 40 yrs
- Absent T2DM and metabolic syndrome
- Low FIB-4, NFS
- Normal or elevated ALT
- Fibroscan < 5 kPa
  - Most likely steatosis only
  - If non-invasive profile indeterminate
  - Obtain liver biopsy and combine results with non-invasive tests

Intermediate risk profile:
- BMI > 29.9 kg/m²
- Multiple metabolic syndrome features
- FIB-4 < 3, NFS 1.454 – 0.676
- Elevated ALT
- Fibroscan 6 – 10 kPa
  - Possibly NASH with F < 3

High risk profile:
- Age > 50 yrs
- T2DM
- FIB-4 > 3, NFS > 0.676
- Elevated ALT
- Fibroscan > 10 kPa
  - Most likely NASH with F3 – F4

Algorithm 1: Evaluation of NAFLD
Non-pharmacological management in the form of healthy lifestyle modifications is the cornerstone in management of NAFLD and prevention of its progression. A comprehensive lifestyle approach to management of NAFLD focuses on three key areas; weight loss, dietary modifications and exercise which in combination will provide the optimum benefit in all patients with NAFLD. The sustainability and consistency of this lifestyle approach over a long period of time should be ensured through persistent motivation and cognitive behavioral therapy.

1.1 Weight Loss

Weight loss has shown a significant improvement of clinical and histological parameters of NAFLD. 5-7% weight loss will result in resolution of steatosis. 7-10% weight loss will result in resolution of steatohepatitis. More than 10% weight loss will result in regression of fibrosis. Thus, a target weight loss of at least 5-10% is recommended to be achieved via a combination of diet and exercise (28).

Degree of weight reduction in an individual is positively associated with the resolution and improvement of liver histology (Figure 6) (35,36,37,38).

1.2 Dietary modifications

The primary aim of dietary modifications is to achieve the target weight loss through a hypo-caloric diet. However, macronutrient and micronutrient composition in diet have also shown to improve biochemical and histological manifestations of NAFLD independent of weight loss.
Figure 5: Comprehensive lifestyle approach to NAFLD management

Figure 6: Effect of weight loss on histological improvement of NAFLD
1.3 Exercise and Physical Activity

Moderate-intensity exercise for 30 – 60 minutes on 3–5 days per week is recommended (28, 41). However, the intensity, duration and type of exercise should be individualized based on patient’s baseline cardiovascular fitness, preference and lifestyle. (Algorithm 2)

Exercise helps to reduce NAFLD progression by reduction of mean hepatic triglyceride composition, peripheral adipose tissue volume, free fatty acid concentration and increase of hepatic glucose sensitivity. The level of cardiovascular fitness at baseline is shown to be the most important factor to affect the degree of hepatic steatosis and it is shown to predict the improvement in NAFLD following lifestyle interventions (44). Benefits of exercise in NAFLD depend on the duration, intensity and type of exercise, independent on the degree of weight loss. Vigorous intensity exercise (Annexure 1) is beneficial in reducing the likelihood of developing NASH and its progression and moderate intensity exercise has shown to have some benefits as well (45,46). Aerobic exercise and resistant training have shown similar benefits in reduction of progression of NASH (47). Apart from improvement of NAFLD, exercise leads to reduction in the overall cardiovascular risk.

| Eat more | Avoid/ minimize |
|----------|-----------------|
| • A variety of vegetables (3-5 servings per day) | • Fast food |
| • Fruits (2-4 servings per day) | • Oversized food servings |
| • Whole grains | • Food items with high calories (eg: cake, ice cream) |
| • Nuts | • Sugar sweetened beverages |
| • Yoghurts | • Unprocessed red meat and Processed meat |
| • Fish (6 Oz per day), cooked in healthy methods | • Salt |
| • Legumes (4 servings per week) | • Alcohol |

Figure 7: Advices to patients.
### Table 4. Non - Recommendations for dietary and lifestyle interventions

| Dietary interventions        | Mechanism of benefit                                                                 | Recommendation                                                                                   |
|-----------------------------|--------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| Hypo-caloric diet           | Calorie restriction drives weight loss and the reduction of liver fat, independent of the macronutrient composition of the diet. | 500-1000 kcal energy deficit per week is recommended to induce 0.5 to 1 kg of weight loss. (28) |
| **LOW CARBOHYDRATE (<40%) DIET** | **BENEFITS OF A LOW CARBOHYDRATE DIET**                                                 | • Either a low carbohydrate or a low fat diet is recommended as both types of diets have shown similar benefits. The choice can be based on patient's preference and feasibility(39) |
| Low carbohydrate diet: calories should be replaced with MUFA, and proteins from fish, meat, nuts and legumes. | • Reduces glycemic load • Reduces insulin resistance • Reduces triglycerides and increases HDL |                                                                                  |
| **LOW FAT (<30%) DIET**     | • Low fat diet: calories should be replaced with low glycemic index food items and protein containing food. |                                                                                  |
| Minimize fructose containing food | Fructose metabolism has shown to increase lipogenesis, hepatocyte steatosis, and oxygen free radical production (40). | • Sugar sweetened beverages with high fructose corn syrup (eg: soft drinks) should be minimized or avoided |
| Minimize / avoid fast food  | Food items with high energy density, large portion size, high carbohydrate content, low fibre, high fructose content, red meat and food high in trans-fat will cause over flow of fat in to liver and hepatic inflammation (41). | • Consumption of fast food should be minimized or avoided |

**Lifestyle interventions**

| Alcohol consumption | Should be discouraged as any degree of alcohol will result in progression of fibrosis and poor outcomes(42) |                                                                                           |
|---------------------|-----------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|
| Coffee consumption | • Regular black, unsweetened drip coffee 2-4 cups has shown to improve liver enzymes, reduce the risk of NAFLD, liver fibrosis and HCC(43). | • Current evidence is inadequate to provide a strong recommendation but can be used as an adjunct |
| Sleep               | • 7-8 hours of adequate sleep will be beneficial                                                                 | • Current evidence is inadequate to provide a strong recommendation but can be used as an adjunct |
Algorithm 2: Decision making on the exercise regimen in NAFLD

Algorithm 2: Decision making on the exercise regimen in NAFLD. *annexure 2
1.4 Bariatric (Metabolic) intervention

Bariatric intervention (endoscopic or surgical) could be considered in patients aged between 18-65 years with a BMI ≥ 30kg/m² with NAFLD. Although not to be used solely for the treatment of NAFLD, bariatric surgery can be useful in management of obese patients with other comorbidities or indications.

Weight reduction is associated with significant improvement in liver histology in patients with NAFLD by several postulated mechanisms (Figure 7) (48). Bariatric surgery is more efficacious in achieving weight loss of 10 to 30% in morbidly obese patients when compared to diet, lifestyle modifications and anti-obesity medications (49). Bariatric surgery related weight loss resolved NASH in up to 85% of patients (50, 51, 52) and improved liver fibrosis in 34% at 1 year post operatively (50). NAFLD is considered as an important comorbidity when deciding on bariatric surgery in morbidly obese individuals (6, 10, 11). The presence of cirrhosis is a relative contraindication for bariatric surgery, as it might lead to increased mortality (48, 53, 54).

Pharmacologic management

Liver-directed pharmacological therapies are only considered for patients with NASH with or without advanced fibrosis. Pharmacological treatment lack evidence in phase III trials, hence not approved for NAFLD by any regulatory authorities. Several categories of pharmacological treatments are available with variable degree of evidence (Table 5). Off label use of pharmacologic therapy might be considered in following stages of NAFLD depending on the excess mortality (27, 55) safety and tolerability. 1. NASH with fibrosis. 2. NASH with high necro-inflammatory activity. 3. NASH with increased risk of progressing to fibrosis (Age >50 years, Diabetes mellitus, Metabolic syndrome, persistently increased ALT).
| Medication | Remarks | Adverse effects | Recommendations |
|------------|---------|----------------|-----------------|
| **Pharmacologic agents with proven benefits** | | | |
| **Hepato-protective agents** | | | |
| Antioxidant Vitamin E | • Reduction in aminotransferases  
• Improvement in steatosis, inflammation and ballooning  
• Resolution of steatohepatitis in a proportion of non-diabetic adults with NASH  
• No effect on hepatic fibrosis (56,57) | • May increase risk of prostate cancer, hemorrhagic stroke and all-cause mortality | • Recommended for biopsy proven NASH in non-cirrhotic and non-diabetics for maximum duration up to 2 years (800 IU/daily) |
| **Anti-diabetic agents** | | | |
| Thiazolidinedione (PPAR, agonist) | Pioglitazone (58) | • Improvement in liver histology including the fibrosis score and arresting disease progression  
• Improvement in insulin resistance and transaminase levels  
• Shown benefits in both patients with diabetes and without diabetes | Concerns regarding weight gain, congestive cardiac failure, increased risk of bladder cancer and fracture | • Recommended for biopsy proven NASH after discussing risks and benefits  
• Not recommended for NAFL alone |
| **Pharmacological agents with NO proven benefits** | | | |
| Metformin | • Improvement in insulin resistance but no improvement in liver histology (59)(60)  
• Reduces HCC risk (61) | Gastro-intestinal effects | NOT recommended for NAFLD alone |
| Glucagon-like peptide-1 analogue | Liraglutide (62): histological resolution of NASH | Gastro-intestinal effects | Limited evidence to recommend at present |
| SGLT2 inhibitors | Empagliflozin (63): reduces liver fat | Volume depletion  
Genito-urinary infections | Inadequate evidence |
| Ursodeoxycholic acid | • Has shown reduction in transaminases without a histological improvement | | NOT recommended for treatment of NAFLD (63) |
| Omega-3 fatty acids | • Have not shown significant effects on transaminases or liver histology | | NOT recommended for treatment of NAFLD (64,65,66). |
| Statins | | | Not recommended for the treatment of NAFLD but can be safely used to treat associated dyslipidemia |
| **Ongoing Phase III trials** | | | |
| Obeticholic acid (OCA) (REGENERATE) | • Has shown promise in improve liver histology (NAFLD activity score) without worsening fibrosis | | Further studies on clinical outcomes are awaited (67) |
| Elafibranor (RESOLVE-IT) and Cenicriviroc (CENTAUR) | • Shown promise by improving liver histology (NAFLD activity score) without worsening fibrosis | | Further studies on clinical outcomes are awaited |
Management of risk factors and associations

Management of type 2 diabetes mellitus, dyslipidemia and metabolic syndrome according to available guidelines is of paramount importance to reduce the associated cardiovascular risk. Apart from the lipid lowering effects and cardiovascular risk reduction, statins have shown benefits in improving liver histology including fibrosis (68). Statins are safe to be used in patients with less than 3 fold elevation of transaminases, however routine prescription is not recommended in patients with decompensated cirrhosis and acute liver failure(69),(70). In addition to well established cardiovascular disease prevention, aspirin has shown to reduce NAFLD related fibrosis (71).

Liver Transplantation

NASH poses unique challenges in liver transplantation. NASH-related cirrhosis is the fastest growing indication for liver transplantation worldwide (72). At present, NASH related cirrhosis is the most common indication for liver transplant in Sri Lanka (73). Deceased and live donor grafts will be limited by the increasing prevalence of NALFD in the general population(74). When compared to non-NASH cirrhosis liver transplant recipients, NASH cirrhosis recipients show similar survival rates at 1, 3, and 5 years. However, they are more likely to die from cardiovascular diseases or sepsis(75). Recurrence of NASH in the graft following liver transplant is not uncommon(76).

Pre-transplant considerations

A transplant recipient with NASH tends to be older, with higher BMI and metabolic comorbidities(77). Obesity is strongly associated with sarcopenia, which is an independent predictor of post-transplant mortality and graft loss(78). When corrected for ascites, higher BMI does not appear to independently confer an increased risk of mortality or allograft failure(78). Considering the high cardiovascular risk, non-invasive and invasive cardiac assessment is recommended as appropriate (79). Both statins and aspirin could be safely used in patients with decompensated cirrhosis and coronary artery disease undergoing liver transplant evaluation (80). Outcomes of NASH-related or cryptogenic cirrhosis appear to be similar to that of alcohol-related cirrhosis without liver transplantation (81).

Post-transplant considerations

Immunosuppressive protocols which include short term and low dose steroids and calcineurin-inhibitors are preferred (77). NASH cirrhosis liver transplant recipients are at high risk of metabolic syndrome, recurrent/ de novo NAFLD and cardiovascular diseases in comparison to general population(82). All transplant recipients should be counselled to continue adherence to the life style modifications.

Recurrent and de novo NAFLD

De novo (20-40%) and recurrent (30-100%) graft steatosis after liver transplant is common(83). Recurrent disease may present more frequently and may progress more rapidly than de novo disease, but the development of allograft NASH cirrhosis is rare (<2% at 10 year follow up)(84). Management is similar to native NAFLD(85).

Donor Hepatic steatosis

When persons with NAFLD are considered for liver allograft donation, severely (>60 %) steatotic grafts are associated with increased risk of poor graft function, whilst moderate - severe (>30 %) steatotic grafts are associated with reduced graft survival(85).

Follow up The optimal follow-up of patients with NAFLD is yet to be determined. Therefore, follow up should be individualized considering the risk of progression, and underlying metabolic conditions. Monitoring should include routine biochemistry (ALT, AST), assessment of co-morbidities, complications and non-invasive monitoring of fibrosis.

Follow up should be every three to six months if major therapeutic changes are done. Six-monthly for patients with advanced fibrosis. Six to twelve monthly, if stable on therapy. Yearly, if young and having low risk of fibrosis. Patients with NASH-related cirrhosis should be offered standard care for cirrhosis in addition to management of comorbidities.

Key recommendations

1. Establish the diagnosis of NAFLD

Ultrasound, hepatic panel, non-invasive markers of liver disease severity

Rule out other causes of fatty liver

2. Establish metabolic syndrome and cardiovascular (CV) risk
Obesity, Hypertension, T2DM, Dyslipidemia, CV risk factors

3. Assess lifestyle and co-morbidities

Daily activity, exercise, dietary history, alcohol and smoking habits, medical co-morbidities and current medications

4. Staging of NAFLD/ NASH/ Fibrosis severity

Non-invasive markers of fibrosis (FIB-4, NFS, transient elastography)

Liver biopsy to exclude secondary fatty liver, fibrosis staging in high risk

5. Therapeutic approaches via a MDT

Weight loss > 5-10% of body weight (dietary and exercise counselling)

Pharmacological modification for each metabolic syndrome component

Liver directed therapies for NASH or established fibrosis

Bariatric intervention in selected patients Appropriate management of NASH-related cirrhosis

6. Follow up

3-6 months if major therapeutic changes are done. 6-monthly for patient with advanced fibrosis. 6-12 monthly if stable on therapy. Yearly if young and low risk of fibrosis.

List of abbreviations

ALP  Alkaline Phosphatase
ALT  Alanine Aminotransferase
AST  Aspartate Aminotransferase
BAT  Brown adipose tissue
BMI  Body Mass Index
CVD  Cardiovascular disease
DNL  De novo lipogenesis
ESLD  End Stage Liver Disease
FC  Free cholesterol
FFA  Free fatty acids
FIB-4  Fibrosis-4
GLP-1  Glucagon like peptide 1
GNG  Gluconeogenesis
HCC  Hepatocellular carcinoma
HS  Hepatic steatosis
HDL  High density lipoproteins
IR  Insulin resistance
IHD  Ischaemic heart disease
LDL  Low density lipoprotein
MBOAT7 Membrane bound O-acetyltransferase domain containing 7
MDT  Multidisciplinary team
NAFL  Nonalcoholic fatty liver
NAFLD  Non-alcoholic fatty liver disease
NAS  NAFLD Activity Score
NASH  Nonalcoholic steatohepatitis
NFS  NASH fibrosis score
PNPLA3 Patatin-like phospholipase domain containing protein 3
PPARY Peroxisome proliferator activated receptor gamma
Se P Selenoprotein P
SGLT2 Sodium-glucose co-transporter-2
T2DM Type 2 diabetes mellitus
TG Triglyceride
TM6SF2 Transmembrane 6 Superfamily Member 2
USS Ultra sound scan
VCTE Vibration controlled transient elastography
VLDL Very low density lipoprotein
WAT White adipose tissue

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**Annexure 1 – Intensity of exercise**

| Moderate intensity exercise | Vigorous intensity exercise |
|-----------------------------|-----------------------------|
| 3-6 METs                    | >6 METs                     |
| Moderate amount of effort needed | Large amount of effort needed |
| Target heart rate: 50-70% of maximum heart rate | Target heart rate: 70-85% of maximum heart rate |
| Examples                    | Examples                    |
| • Brisk walking             | • Hiking                    |
| • Bicycling slowly (10-12 mph) | • Jogging                   |
| • Badminton                 | • Climbing briskly up a hill|
|                             | • Carrying heavy loads      |
|                             | • Fast bicycling            |
|                             | • Basketball, foot ball     |

Maximum heart rate = 220 - age

**Annexure 2 – Types of exercise**

| Resistance training | Aerobic exercise |
|---------------------|------------------|
| exercise that promotes musculoskeletal fitness rather than cardiovascular fitness. | Any activity using large muscle groups, that is rhythmic in nature and which can be continuously maintained |
| Eg: weight training, pushups, squats, kick backs | Eg: cycling, swimming, brisk walking, running |
| No gold standard measurements for assessing the resistance training adaptations | Gold-standard for measuring physiologic adaptation to aerobic training is maximal aerobic capacity, VO2max, a measure of cardiorespiratory fitness |
| Can target specific muscle types and energy systems | Depends mainly on skeletal muscle's utilization of oxygen through aerobic respiration to produce energy |