The Asia-Pacific Working Party on Nonalcoholic Fatty Liver Disease Guidelines 2017
Part 1: Definition, risk factors and assessment


1 Department of Medicine and Therapeutics, 2 State Key Laboratory of Digestive Disease, and 15 Department of Surgery, The Chinese University of Hong Kong, Hong Kong, China
3 Department of Medicine, University of Malaya, Kuala Lumpur, Malaysia
4 Gastroenterology and Hepatology Unit, The Canberra Hospital, Canberra, Australia
5 Department of Hepatology, Post Graduate Institute of Medical Education and Research, Chandigarh, India
6 Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
7 Xin Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China
8 Department of Diabetology, Kameoka Municipal Hospital, Kameoka, Japan
9 Department of Internal Medicine and Gastroenterology, Tokyo Women’s Medical University, Tokyo, Japan
10 Department of Internal Medicine, Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, Korea
11 Digestive Disease and GI Oncology Centre, Medistra Hospital, Jakarta, Indonesia
12 Hepatitis Research Center, National Taiwan University, Taipei, Taiwan
13 Department of Internal Medicine, Hepatitis Research Center and Graduate Institute of Clinical Medicine, National Taiwan University College of Medicine and Hospital
14 University of Santo Tomas, España Boulevard, Manila, the Philippines

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Correspondence:
Prof Geoffrey C. Farrell
The Canberra Hospital, PO Box 11, Woden, ACT 2606, Australia
Tel: 61-2-6244-2473       Fax: 61-2-6244-3235
E-mail: geoff.farrell@anu.edu.au

Dr Vincent Wong
Department of Medicine and Therapeutics, 9/F, Clinical Sciences Building, Prince of Wales Hospital, 30-32 Ngan Shing Street, Shatin, Hong Kong
Tel: 852-26321205       Fax: 852-26373852
E-mail: wongv@ cuhk.edu.hk

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1. Introduction

Since the publication of the guidelines for the assessment and management of non-alcoholic fatty liver disease (NAFLD) by the Asia-Pacific Working Party on NAFLD in 2007,¹ our understanding of the clinical characteristics and natural history of NAFLD has improved, and there have been developments in the assessment and treatment of NAFLD. It is therefore timely to update the guidelines in light of new evidence.

This document presents the recommendations of the Asia-Pacific Working Party on NAFLD. The exercise was supported by the Journal of Gastroenterology and Hepatology Foundation. Members performed a systematic review of the literature on specified domains of interest, thereby allowing them to provide recommendations on different aspects of the clinical assessment and management of patients with NAFLD. The contents and statements were then discussed through face-to-face meetings and e-mail communications. The statements in this document follow the Grading of Recommendation Assessment, Development and Evaluation (GRADE) approach (Table 1).² The final grading of evidence and recommendations was determined by majority vote.

These guidelines cover various aspects in the management of NAFLD, including diagnosis, screening, assessment and treatment. While most evidence came from studies on adults identified to be at risk of metabolic disorder and after exclusion of other liver diseases, two special populations are included in this document. NAFLD in children and adolescents is becoming increasingly prevalent and may have devastating consequences owing to the long duration of fatty liver disease. In addition, chronic viral hepatitis is highly prevalent in Asia-Pacific countries, and the impact of concomitant fatty liver, a much discussed topic both for hepatitis B and C, is re-evaluated here for its long-term clinical significance and implications for patient care.
2. Definitions

2.1 The need for a definition

A clear, reproducible definition of NAFLD is required for clinical practice and epidemiological studies because there are several causes of fatty liver and steatohepatitis, each with differing management implications and clinical outcomes. An unresolved definitional and semantic challenge is that two or more etiological factors commonly interact to influence the incidence, severity and outcome of fatty liver.

2.2 Established “negative” definition of NAFLD (e.g. American Association for the Study of Liver Diseases [AASLD] 2012)

The current established “negative” definition of NAFLD requires: (a) evidence of hepatic steatosis either by imaging or histology, and (b) absence of other causes of hepatic fat accumulation from conditions such as significant alcohol consumption, hepatitis C, medication use, or hereditary disorders.

While it has been acknowledged that “in the majority of patients”, NAFLD is associated with metabolic risk factors such as obesity, diabetes mellitus and dyslipidemia, this fails to identify over-nutrition (as opposed to established obesity) as pivotal, or to account for the approximately 25% of patients in Asian cohorts who have fatty liver but are not obese. However, the vast majority of such “non-obese NAFLD” patients exhibit insulin resistance. In this respect, it is also critical to note that family history of diabetes (genetic predisposition), and pre-diabetes as well as established diabetes are commonly associated with NAFLD.

Finally, it has now been clearly demonstrated that loss of 10% of body weight (in over-weight persons) completely reverses all elements of non-alcoholic steatohepatitis.
(“NASH”) pathology, including liver fibrosis. This cements the role of over-nutrition in the causation of NAFLD.

2.3 Proposed “positive” definition of NAFLD

Review articles from Europe have tended towards a more positive definition of NAFLD, as did the original Asia-Pacific Guidelines of 2007. The recommended definition for the 11th Revision of the International Classification of Diseases (ICD-11) is:

“NAFLD is characterized by fatty liver (defined as earlier) related to over-nutrition in the absence of excessive alcohol consumption.”

We therefore recommend the following language:

2.1 Non-alcoholic fatty liver disease (NAFLD) is a form of fatty liver disease (as previously defined – see 2007 Guidelines and the 2012 American Guidelines) that can reasonably be attributed to over-nutrition and its complications, such as weight gain, central obesity, insulin resistance, glucose intolerance, atherogenic dyslipidemia and arterial hypertension (metabolic syndrome), particularly in genetically predisposed individuals. For a strict definition of NAFLD, significant (or excessive) alcohol consumption and other diseases must be excluded. However, the interaction between over-nutrition and other liver disorders commonly causing fatty liver disease, including hepatitis C, hepatitis B, alcohol-related liver disease, and haemochromatosis needs to be recognized. (A1)
2.4 Pathological subtypes and outcomes of NAFLD

The majority of cases of NAFLD show steatosis with no or minimal liver inflammation. The term favoured by AASLD for this, non-alcoholic fatty liver (NAFL), has not been adopted by ICD-11 as it seems ambiguous. Specifically, all NAFLD cases have fatty liver, whether steatohepatitis (NASH) is present or not. Instead, if the pathology is known, the terminology should be: “NAFLD without NASH” or “simple steatosis”, “NASH”, and “with or without fibrosis or cirrhosis” for either category.

Between 10 to 25% of NAFLD cases show steatohepatitis i.e., NASH. The hallmarks are conspicuous hepatocyte injury (especially ballooning, apoptosis) and substantial liver inflammation. NASH is more likely to be associated with liver fibrosis than cases showing only steatosis. Notwithstanding the likely importance of NASH in leading to fibrosis, it is the presence of fibrosis (with or without NASH) that predicts progression to cirrhosis in clinical outcome studies. Hepatocellular carcinoma (HCC) is a complication of NAFLD, but not exclusively among cases which progressed to cirrhosis (including cases of “cryptogenic cirrhosis”). Besides, it is unclear if a patient must have NASH before progressing to NAFLD-related HCC.

2.5 Alcohol exclusion criteria

No more than one standard drink/day (i.e. 70 g ethanol/week) for women and no more than 2 standard drinks/day (i.e. 140 g ethanol/week) for men has been used by the National Institutes of Health (NIH) NASH clinical research network (CRN) and widely adopted for clinical studies. The relevance of this standard to the populations in the Asia-Pacific region was discussed in the 2007 Guidelines. The proposed levels of alcohol intake are based on evidence about daily alcohol intake and risk of cirrhosis. The “cut-off” values have been set.
lower than the apparent “threshold levels” so as to avoid the issue of overlap between alcoholic liver disease and obesity, T2DM and metabolic syndrome in progression to cirrhosis. Patients who may be drinking at safe levels at the time of presentation with liver disease may have a past history of chronic excessive alcohol intake for a prolonged period of time, and may have cirrhosis. Life-time alcohol intake is therefore important, and needs to be incorporated into history taking.

3. Epidemiology

3.1 Adults

3.1.1 Prevalence of NAFLD

Over the past three decades, changing Western lifestyles and dietary habits, in addition to relatively high rates of genetic predisposition in several community groups, have increased the prevalence of NAFLD in the Asia Pacific region. Based on hepatic imaging, recent studies suggest that a quarter (95% confidence interval [CI]: 23.3%-31.9%) of the general population in Asia has NAFLD, but the proportion of patients with advanced liver fibrosis diagnosed by transient elastography appears to be low (3.7% among NAFLD patients). Obesity, dyslipidemia, T2DM and metabolic syndrome are established risk factors for developing NAFLD. In addition, several other risk factors for NAFLD have been identified in the Asia Pacific region. These include hypothyroidism, polycystic ovary syndrome, obstructive sleep apnea, hypopituitarism, and hypogonadism.

There may be subtle differences in the phenotype distribution of NAFLD between Asia Pacific and Western countries. Of particular interest are more frequent “lean NAFLD” and the urban-rural differences of prevalence rates of NAFLD in Asia. In addition, Asian people are particularly susceptible, partly owing to body composition differences in fat and muscle,
and genetic susceptibility via predisposition to T2DM, PNPLA3 SNPs and polymorphisms in apolipoprotein 3. On the other hand, the natural history of NAFLD and its progression to cirrhosis and HCC (when this occurs) is over several decades; the fact that NAFLD in Asian countries may be more recent than in North and South America, for example, may also influence the present distribution of disease phenotypes towards the milder end of the pathological spectrum.

3.1.2 Prevalence of NASH and incidence of NAFLD

There are limited studies evaluating the incidence of NAFLD and the prevalence of NASH in the general population. In Japan, pooled regional NAFLD incidence rate estimates are 52.3 (95%CI: 28.1-96.8) per 1,000 person-years. Incident NAFLD is not uncommon among Chinese people who are not obese; for instance, 8.9% of lean subjects developed NAFLD during a 5-year follow-up. Because the diagnosis of NASH requires a liver biopsy, the population prevalence of NASH in Asia is currently unknown. Among Asian liver biopsy series, NASH can be found in 63.5% (95%CI: 47.7-76.8). In natural history studies involving paired liver biopsies, around 25% of patients may progress from simple steatosis to NASH in 3 years.

3.1.3 Prevalence of NASH-related cirrhosis and HCC

NASH is the most common cause of cirrhosis and HCC in patients without other known etiological causes of liver disease worldwide. Thus, 63.3% of formerly designated cryptogenic cirrhosis cases could finally be attributed to NAFLD because cryptogenic cirrhosis is more associated with metabolic syndrome than other causes of cirrhosis. A study from Japan found that 17 of 320 HCC cases (5.3%) were either associated with NASH or had
unknown (“cryptogenic”) etiology. “Cryptogenic” HCC also accounted for 5.4% of all HCCs in Korea. Metabolic syndrome and its components (i.e., obesity, T2DM) are very common in cryptogenic cirrhosis and HCC patients. Recent literature from Asia also suggests a strong association between NAFLD and HCC in non-cirrhotic livers (see comments under Definition). The majority of NASH-related HCC patients either did not have definite cirrhosis or cirrhosis was well compensated (Child-Pugh A), compared to Child B and C cirrhosis with other etiologies. However, data from carefully controlled long-term studies from this region, with better documentation of liver disease, are required to determine the prevalence and incidence of HCC in NAFLD patients, especially in non-cirrhotic NASH patients in Asia. Another general need is to better understand the relative importance of individual host and environmental factors in determining the prevalence of NAFLD and its liver complications in different ethnic groups across geographical areas of the vast Asia Pacific region.

3.2 Children and adolescents

3.2.1 The prevalence of NAFLD in children and adolescents

Estimates of the prevalence of NAFLD in children and adolescents vary widely between epidemiologic studies. Using liver ultrasonography, Tominaga et al. reported the prevalence of NAFLD was 2.6% in 810 Japanese children aged 4 to 12 years. Another study from Shanghai showed the prevalence was 2.1% in 6 to 12 year-old school children in China. To clarify the prevalence of NAFLD in obese children (defined as the body mass index value > 95 percentile by age- and gender- specific cut-off points), Lin et al. reported that 22.8% of 832 obese Taiwanese children and adolescents had ultrasound-defined NAFLD. However, the true prevalence of NAFLD may be underestimated by this method because liver
ultrasonography is relatively insensitive for detecting cases with hepatic fat content below 30%.\textsuperscript{12}

Serum alanine transferase (ALT) is frequently used to assess NAFLD prevalence. The prevalence of elevated ALT levels (> 40 U/L) was 8% in 1,594 adolescents aged 10 to 19 years in the Korean National Health and Nutrition Examination Survey 1998.\textsuperscript{13} A Japanese study of 228 obese children aged 6-15 years reported a prevalence of ALT > 35 U/L of 24.1% (the "normal" value for ALT in general population is likely to be 25.8 U/L in boys and < 22.1 U/L in girls).\textsuperscript{14, 15} There are some limitations when using ALT as a screening measure for NAFLD as the upper limit of normal ALT is not well established and ALT levels do not parallel the histologic severity of NAFLD in children or adults.\textsuperscript{16}

3.2.2 Prevalence of NASH and NASH-related cirrhosis

The standard diagnosis of nonalcoholic steatohepatitis (NASH) relies on liver histologic features. There were no studies to estimate NASH prevalence by this method in Asia-Pacific region. In USA, Schwimmer et al. used autopsy data to assess liver steatosis. They found the prevalence of NAFLD and NASH was 13% and 3%, respectively, among children, regardless of the cause of death.\textsuperscript{17} Another study in Poland surveyed children whose death was caused by trauma; prevalences of NAFLD and NASH were 5.3% and 0.3%, respectively.\textsuperscript{18} NASH-related cirrhosis has been reported in children as young as 10 years of age.\textsuperscript{19}

3.2.3 Geographical difference

A recent meta-analysis reported that the pooled prevalence estimates did not differ by geographical region in general population among children and adolescents. In contrast, in clinical studies of obese population, the prevalence estimates varied by geographical region, being higher in the studies from Asia (62.3%), than studies from Europe (29.8%) and North...
It should be emphasized that diagnostic methods used in different studies could significantly affect NAFLD prevalence estimates.

3.3 Risk factors of NAFLD

Overnutrition and insulin resistance are dominant risk factors for the development of NAFLD (Table 2). The condition of gut microbiota, genetic variations, and epigenetic regulation induced by microRNAs, DNA methylation, histone modification and ubiquitination may alter the susceptibility to NAFLD. Although the prevalence of NAFLD increases with age and with the male gender, the direct relationships among age, gender, and susceptibility to NAFLD remain unsettled.

Fatty liver can also be triggered by exogenous factors including certain medications and malnutrition, although the liver pathology in such cases may be indistinguishable from NAFLD secondary to overnutrition and obesity.

3.3.1 Overnutrition and insulin resistance

Overnutrition or inappropriate diet, such as excessive carbohydrate intake and/or excessive fat intake, induce insulin resistance and body weight gain. Excessive carbohydrate intake, and/or excessive fat intake also lead to increased circulating concentrations of both glucose and free fatty acids. Moreover, insulin resistance reduces glucose uptake by adipose tissue and muscle, and reduces the hydrolysis of triglycerides in adipose tissue.

Insulin programs hepatic uptake of free fatty acid and free cholesterol, which consist of the majority of liver fat. de novo lipogenesis is also increased by insulin, which leads to an increased conversion of glucose to fatty acids in the liver. Thus, insulin resistance with
resultant hyperinsulinemia, combined with the increased circulating concentrations of both

glucose and free fatty acid, contributes to an excessive accumulation of neutral lipids in the

liver.31-33

It is widely accepted that obesity/over weight is the most significant risk factor for

incident NAFLD.34-38 However, weight gain that has not yet led to obesity is also an important
determinant of NAFLD incidence.31,39 Thus, body weight gain after 20 years of age as well as
body weight gain from baseline to onset are both risk factors for incident NAFLD, in both

obese and non-obese individuals.40

3.3.2 Gut microbiota

Several studies in mice indicate that the gut microbiome influences both sides of the

energy-balance equation by contributing to nutrient absorption and increasing

metabolic-endotoxemia, which increases hepatic steatosis.41-43 Small intestinal bacterial

overgrowth increases intestinal permeability23 and could induce endotoxemia.44 Although a

specific gut microbiota might be involved in incident NAFLD, no consensus has yet been

reached about this.

3.3.3 Genetic variations

The G allele of PNPLA3 rs738409 is associated with the degree of hepatic steatosis,45

while the T allele of PNPLA3 rs6006460 is associated with lower hepatic triglyceride

content.45 The variant of TM6SF2 is associated with the hepatic triglyceride content.46 A

relationship between the gene polymorphisms of APOC3 and hepatic triglyceride content

has been reported47, but so have contrary findings; a meta-analysis found no significant

association between APOC3 polymorphisms and risk of NAFLD.48
3.4 Natural History

NAFLD is associated with an increase in the standardized mortality ratio compared with the general population due to an increased liver–cardiovascular-related mortality rate.\textsuperscript{49-54} The most common causes of death in patients with NAFLD are cardiovascular disease and malignancy, followed by liver-related disease. Overall NAFLD appears to be slowly progressive with liver-related morbidity and mortality occurring in a small number of patients. The reported risk factors for the development of advanced fibrosis or cirrhosis are advanced age, diabetes, morbid obesity, and transaminase elevation.\textsuperscript{55-58} Prospective follow-up studies for the incidence and remission of NAFLD in the general population showed that the incidence rate of NAFLD was around 7-20% during a 1-7 year follow-up period, and 16-37% of patients with NAFLD had remission during that period. It is well known that weight gain is closely related to NAFLD development, and weight loss is associated with NAFLD remission.

3.4.1 Histological progression

It is generally agreed that simple steatosis is mostly a benign, non-progressive clinical entity, while NASH can progress to cirrhosis, which in rare cases gives rise to HCC. However, recent paired-biopsy studies have demonstrated that simple steatosis has the potential to progress to NASH with development of fibrosis,\textsuperscript{8, 59-61} and that the presence and severity of fibrosis, regardless of the diagnosis of NASH, dictates the long-term prognosis.\textsuperscript{50, 62, 63} According to a systemic review and meta-analysis of paired-biopsy studies, the annual fibrosis progression rate in patients with simple steatosis was 0.07 stages, compared with 0.14 stages in patients with NASH.\textsuperscript{61} Fibrosis progresses rapidly in 20% of patients. A histological risk factor for such progression is more extensive necroinflammatory change on
baseline liver biopsy. The characteristic features of NASH disappear in advanced cirrhosis, a phenomenon referred to as “burned-out NASH”.

3.4.2 Cirrhosis and liver decompensation

Previous studies have reported that patients with cirrhotic NASH/NAFLD showed a similar survival rate to patients with cirrhosis caused by the hepatitis C virus, although the rate of development of HCC was lower (5-year HCC development rate: about 10%, 5-year survival rate: 70-80%).

3.5 NASH-related HCC

NAFLD can lead to cirrhosis and result in HCC. Up to 30% of HCC can be attributable to cryptogenic cirrhosis, the majority of such cases are believed to be due to NASH. Cross sectional studies in Asian countries such as Malaysia, Japan and Korea suggest that the contribution of NASH to HCC is lower than in the West, and is in the region of 7-16%.

The incidence of HCC in NAFLD is highest in patients who have cirrhosis. In Japanese cohorts, the retrospective annual incidence of developing HCC among 6,508 NAFLD patients was 0.043%, but it was 25 times more likely among those with advanced fibrosis. Among cirrhotics, the incidence of HCC was 11.3% in 5 years. In addition, obesity and diabetes mellitus are independent risk factors for HCC, and increase the risk of HCC with other disorders (e.g. hepatitis B, hepatitis C) 10-fold. The obesity and diabetes pandemic has caused a sharp rise in incidence of NASH-related HCC, which has now become the most rapidly rising cause for liver transplantation in the US. Data from South Korea corroborate the same trend where NAFLD HCC has risen from 3.8% to 12% over the last decade.
There is growing evidence that HCC can occur in patients with NASH without development of liver cirrhosis.\(^\text{79}\) Japanese series have reported that 38-49% of NASH HCC cases do not show evidence of liver cirrhosis\(^\text{71, 75, 80}\), and the risk of non-cirrhotic HCC appears to be highest with NAFLD compared to other aetiologies\(^\text{81}\).

**Recommendation Statements**

3.1 NAFLD-related HCC is becoming increasingly prevalent in Asia. (B1)

3.2 The risk of HCC with NAFLD is directly related to the degree of liver fibrosis, but HCC can occur in non-cirrhotic patients. (C1)

**4. Diagnosis**

NAFLD should be suspected as the cause of liver disease in any patient who is overweight and in whom hepatitis B or C, alcoholic liver disease, autoimmune liver diseases and inherited metabolic diseases have been excluded. Liver disease may present with abnormal liver tests (usually minor increases in ALT and gamma-glutamyl transpeptidase); a clear relationship between these changes and fluctuations in body weight is a clue to diagnosis. Hepatic imaging (usually ultrasonography) should be used to confirm steatosis. If negative, other techniques, such as controlled attenuation parameter by transient elastography, may provide supporting data.

Exclusions require meticulous history taking for lifetime and current alcohol exposure. A lifestyle history, including trajectory of body weight since young adulthood and recently, waist expansion, eating habits, sedentary occupation and level of physical activity is a prerequisite to considering NAFLD diagnosis. A personal or family history of T2DM,
premature vascular disease, atherogenic dyslipidemia and high blood pressure (metabolic syndrome), fatty liver and cirrhosis is often informative.

In many cases, diagnosis could be made with positive recognition of risk factors for NAFLD, exclusion of other disorders, and documentation of fatty liver by hepatic imaging. If biochemical changes normalise with lifestyle intervention and weight loss, a diagnosis of NAFLD is very likely. On the other hand, recommendation for liver biopsy will depend on the level of confidence that other conditions have been excluded (such as autoimmune hepatitis, drug-related liver disease), and whether approaches to reversing NAFLD other than weight reduction by lifestyle intervention or obesity surgery are being considered, such as entry into a clinical trial of novel pharmacological agents.

Exclusion criteria:

i. Significant alcohol intake [> 7 standard alcoholic drinks/week (70 g ethanol) in women, > 14 (140 g) in men]

ii. Hepatitis B and C by serologic and virologic criteria

iii. Drug-induced liver disease, including herbal medicines and dietary supplements

iv. Autoimmune liver disease – including autoimmune hepatitis (3 subtypes), celiac disease, primary biliary cholangitis, primary sclerosing cholangitis

v. Metabolic liver disorders: Wilson’s disease, alpha-1-antitrypsin deficiency, hemochromatosis, glycogen storage disorders, cholesterol storage disorders, etc

Diagnostic workup:

i. Conventional liver biochemistry (include ALT and AST); platelet count

ii. Hepatic ultrasonography. If no evidence of steatosis, consider MRI liver (more sensitive and quantitative but expensive).
(Metabolic tests for risk factors are discussed in Section 6.6.)

Fibroscan (transient elastography [TE]) or other modalities may be used to determine liver stiffness. Although the cut-offs for NASH versus not NASH and for various stages of fibrosis have not yet been agreed to, TE can be a basis for confirming the potential benefits of lifestyle intervention by observed changes, including normalization of liver stiffness. In addition, controlled attenuation parameter measurement is an alternative approach to steatosis quantification, as discussed in detail in Section 6.

In patients with abnormal liver tests and/or liver stiffness measurement, the options are immediate liver biopsy or retesting after lifestyle changes. This is considered in detail in Section 6.4.

5. Screening

NAFLD is the most common cause of chronic liver disease and is estimated to affect up to 30% of the general population. However, only a small proportion of the general population has severe liver disease due to NAFLD. In a population-based study on 922 subjects in Hong Kong, NAFLD (based on proton-magnetic resonance spectroscopy) was observed in 27.3% while advanced fibrosis (based on liver stiffness measurement) was found in only 3.7%. Nevertheless, subjects found to have NAFLD on population screening may benefit from lifestyle interventions, as well as assessment for, and treatment of, other components of the metabolic syndrome to reduce the risk of cardiovascular disease. However, the cost effectiveness of such an approach is unknown. On the other hand, the prevalence of NAFLD and severe liver disease is remarkably high among patients with diabetes mellitus and obesity. In a study on 1,918 patients with diabetes mellitus using transient elastography, the proportions of patients with increased controlled attenuation
parameter (consistent with NAFLD) and liver stiffness measurement (consistent with advanced fibrosis) was 73% and 18%, respectively.\textsuperscript{84} In a separate study, the prevalence of NAFLD (based on proton-magnetic resonance spectroscopy) and advanced fibrosis (based on liver stiffness measurement) was 61% and 19%, respectively, among obese subjects.\textsuperscript{85} In another study on 102 patients with morbid obesity undergoing bariatric surgery, NAFLD, NASH and advanced fibrosis was observed in 82%, 78% and 16%, respectively.\textsuperscript{86} These groups of patients would fulfil most of the classic criteria for screening.\textsuperscript{87} While the current lack of an effective drug treatment is a stumbling block to strongly recommending community screening (whether all or those with risk factors), the results of lifestyle intervention with reduction of 10% of body weight are now such that it can be reasoned that those affected by NAFLD, with their increased standardized mortality largely attributable to cardiovascular disease and common cancers, need to be appraised of the merits and importance of interrupting the health consequences of NAFLD.

Serum aminotransferase levels are not useful for screening for NAFLD as they may be normal in patients with severe liver disease due to NAFLD \textsuperscript{88}, and they may be increased in some patients with only simple steatosis. Ultrasonography is a reasonable screening tool. Using a scoring system, ultrasonography was found to have excellent sensitivity (92%) and specificity (100%) for the diagnosis of NAFLD.\textsuperscript{89} However, it is operator dependent and may be less accurate for mild fatty liver.\textsuperscript{90} The controlled attenuation parameter using fibroscan has been shown to be excellent for the detection of significant hepatic steatosis, and may be useful as a screening tool for NAFLD, where available, as well as for assessing progress (response to lifestyle intervention and weight loss).\textsuperscript{91} Moreover, liver stiffness measurement is performed simultaneously, allowing assessment of the severity of liver disease at the same setting.
Despite the above, there exists knowledge gaps in the natural history of NAFLD/NASH, optimal screening tool, long-term outcomes of treatment and cost-effectiveness of screening (Table 3). These preclude a concrete recommendation on screening for NAFLD/NASH.

Recommendation Statements

5.1 Screening of NAFLD may be considered in at risk groups such as patients with T2DM and obesity. (B2)

5.2 Ultrasonography is a reasonable screening tool for NAFLD, but will not detect many cases of minor steatosis. (B1)

5.3 Transient elastography may be used as a screening tool where available. (B2)

5.4 Patients with NAFLD detected by screening should receive advice and support for lifestyle interventions to reduce the risk of onset of T2DM and cardiovascular disease, and to resolve fatty liver disease. (A1)

5.5 Patients with NAFLD detected by screening should be assessed for other components of metabolic syndrome (including T2DM, atherogenic dyslipidemia and arterial hypertension) and be treated accordingly. (A1)

5.6 Patients with NAFLD detected by screening should be assessed for severity of liver disease. (B1)
6. Assessment

6.1 Liver histology

6.1.1 Who should undergo liver biopsy?

Liver biopsy is essential for the diagnosis of NASH, as opposed to the other liver phenotypes of NAFLD. However, it is an expensive and invasive procedure with a very low risk of morbidity and mortality. Additionally, sampling errors and variability in interpretation by pathologists may occur. Moreover, in clinics with a large number of referred patients or in a community setting, a liver biopsy is not logistically suitable as a general diagnostic procedure. Accordingly, liver biopsies may strongly be advocated for patients with NAFLD who are suspected to have co-existing chronic liver diseases, and/or when there is a need to distinguish NASH from other chronic liver diseases, especially autoimmune hepatitis. The development and application of new imaging modalities and diagnostic scores can reduce the clinical need for liver biopsy.

6.1.2 What histological features should be examined and reported?

NASH is defined as the presence of hepatic steatosis, inflammation, and hepatocyte injury (ballooning degeneration). Simple steatosis encompasses steatosis alone or steatosis with inflammation. The histological check-list is as follows: steatosis, lobular and portal inflammation, ballooning degeneration, Mallory-Denk bodies, megamitochondria, lipogranulomas, iron granules, glycogenated nuclei, acidophilic bodies, veno-occlusive lesions, pericellular fibrosis, and degree of fibrosis. Degree of fibrosis and portal inflammation have been reported to be very important features for prognosis but not necessary for the diagnosis for NASH. In children, steatosis and portal-based chronic
inflammation are more prominent than in adults, and hepatocellular ballooning and Mallory-Denk bodies are not conspicuous. 

6.1.3 What kind of histological staining should be performed?

The minimum staining includes hematoxylin and eosin, picrosirius red or Mallory’s stain for the detection of fibrosis, and Perls staining for hemosiderosis.

6.1.4 Which scoring system, if any, should be used?

In 2005, the NASH Clinical Research Network Pathology Committee developed and validated the NAFLD Activity Score (NAS) as a semi-quantitative instrument to judge treatment responses and disease progression in clinical studies. NAS was not developed to diagnose NASH; it was developed as a potential endpoint for clinical trials, but even in this respect has now been replaced by the FDA and AASLD recommended endpoint of NASH reversal without fibrosis worsening. The NAS system is the un-weighted sum of the scores for steatosis (0-3), lobular inflammation (0-3), and ballooning degeneration (0-2). A score of greater than or equal to 5 correlates with a diagnosis of NASH; scores less than 3 correlate with “non-NASH”; and scores of 3 or 4 are regarded as borderline. With regard to fibrosis, stage 1 refers to perisinusoidal fibrosis in the perivenular area (delicate <1A>, or dense <1B>). Detection of portal fibrosis without perisinusoidal fibrosis is defined as 1C. Stage 2 is characterized by perisinusoidal and portal/periportal fibrosis. Stage 3 is defined as bridging fibrosis, and stage 4 as cirrhosis.

The recently reported fatty liver inhibition of progression (FLIP) algorithm and steatosis, activity, and fibrosis (SAF) score increase observer agreement. The FLIP algorithm is based on semiquantitative evaluation of steatosis, hepatocellular ballooning, and lobular
inflammation for segregating normal liver, NAFLD, and NASH. The SAF score consists of the semiquantitative scoring of steatosis (S), activity (A), and fibrosis (F). The activity score consists of ballooning degeneration and lobular inflammation. It is important to note that steatosis does not include activity, but this is reported separately in the SAF score; this is because the degree of steatosis is not a histological marker of ongoing liver damage. Fibrosis staging basically relies on the Kleiner classification. Based on the distinctive histological pattern, a specific histological score – the Paediatric NAFLD Histological Score (PNHS) – has been validated for better classification of children with/without NASH.

6.2 Non-invasive tests of hepatic steatosis (Table 4)

6.2.1 Prediction models

Several prediction models composed of common clinical and laboratory parameters have been used in clinical studies. While none of these allow precise estimation of liver fat content, they collectively point to simple biochemical indices for clinicians to consider the presence of NAFLD. In fact, the extent of steatosis (or its biochemical equivalent of total liver fat content) may not be relevant to the outcome of NAFLD or its sub-type of NASH (see sections 3.4 and 6.1).

Fatty liver index is derived from serum triglyceride and gamma glutamyl transferase (GGT) levels, body mass index (BMI), and waist circumference. NAFLD liver fat score estimates liver fat content (in percentage) with a formula consisting of metabolic syndrome, type 2 diabetes, fasting serum insulin, aspartate aminotransferase (AST), and the AST/ALT ratio. SteatoTest is a complex logistic regression model of 12 parameters: α2-macroglobulin (A2M), apolipoprotein A-1 (ApoA1), haptoglobin, total bilirubin, GGT,
cholesterol, triglycerides, glucose, age, gender, and BMI. The issue of steatoTest is some of the parameters (e.g. A2M and ApoA1) may not be readily available in local laboratories.

6.2.2 Abdominal ultrasonography

Abdominal ultrasonography is the most common first-line imaging modality for patients with elevated liver enzymes or suspected NAFLD. An increase in the echogenicity of the liver parenchyma appearing brighter than the cortex of the kidney, intrahepatic vessels blurring and deep attenuation are the typical imaging features of fatty liver. A 6-point score based on these ultrasonographic features was found to correlate well with histologic steatosis. However, ultrasonography does not perform well in morbidly obese patients and may miss the diagnosis (because of insensitivity) if steatosis is ≤30%.

6.2.3 Controlled attenuation parameter by FibroScan

Controlled attenuation parameter (CAP) measures ultrasound attenuation (go and return path) using signals acquired by the M probe or XL probe of a FibroScan machine. CAP has demonstrated satisfactory diagnostic performance in detecting steatosis, with area under receiver operating characteristics curves (AUROC) ranging from 0.80 to 0.97 for steatosis ≥11%, 0.81 to 0.95 for steatosis ≥34%, and 0.66 to 0.93 for steatosis ≥67%. FibroScan has the advantages of being painless, rapid (usually less than 5 minutes) and user-friendly. CAP can be measured simultaneously with liver stiffness (see below) and thus may be used to diagnose NAFLD by confirming the presence of steatosis, and to assess its severity (albeit the uncertainty remains regarding the “cut-offs” for NASH vs SS, and for advanced fibrosis or cirrhosis vs no or other degrees of fibrosis – see earlier section?)
6.2.4 Magnetic resonance imaging (MRI)

Proton magnetic resonance spectroscopy (H\textsuperscript{1}-MRS) measures proton signals from the acyl groups of hepatocyte triglyceride stores directly. MRS accurately measures intrahepatic triglyceride content (IHTG); the results correlate well with histological assessments of hepatic steatosis.\textsuperscript{119} An IHTG cutoff of 5-5.5% is often used to define fatty liver with high sensitivity.\textsuperscript{83}

MRI-estimated proton density fat fraction (MRI-PDFF) is an imaging-based biomarker that allows fat mapping of the entire liver\textsuperscript{120}, whereas MRS-PDFF provides a biochemical measure of liver fat in small regions of interest.\textsuperscript{119} MRI-PDFF is potentially more suitable to quantify changes in liver fat in clinical trials as it is more sensitive than the histology-determined steatosis grade in quantifying changes in the liver fat content.\textsuperscript{121} MRI-PDFF has an AUROC of 0.95 for steatosis $\geq$67%; nonetheless the PDFF results were affected by the presence of fibrosis.\textsuperscript{120} Despite their high degree of accuracy, the availability and cost of MR-based techniques are the key hurdles in limiting their applicability, especially to the general population.

6.3 Non-invasive tests of NASH

6.3.1 Cytokeratin-18 fragment

Plasma cytokeratin-18 fragment (CK-18) reflects the degree of hepatocellular apoptotic activity, a characteristic feature of NASH.\textsuperscript{122} Three ELISA-based CK-18 assays have been developed to assess NAFLD. The M30 assay detects hepatocyte apoptosis through the identification of a caspase-cleaved fragment of CK-18. In contrast, both M65 and M65ED assays detect total cell death through the identification of both caspase-cleaved and uncleaved CK-18.\textsuperscript{123}
CK-18 level is significantly increased in NASH.\textsuperscript{124} It has demonstrated good diagnostic accuracy for NAFLD versus healthy livers, but less satisfactory accuracy for NASH versus simple steatosis.\textsuperscript{125,126} The latter is arguably the greater diagnostic need in clinical assessment. The test was also criticized for limited sensitivity at a cut-off value of 165 U/L, making it inadequate as a screening test for staging NASH.\textsuperscript{127} A meta-analysis of 10 studies showed that CK-18 fragments had an AUROC of 0.8 to diagnose NASH versus non-NASH.\textsuperscript{128} Two other models combining CK-18 with hyaluronic acid\textsuperscript{129}, or soluble Fas\textsuperscript{130}, showed better predictive value for NASH versus non-NASH in patients with NAFLD. As the diagnostic accuracy is modest, CK-18 is unlikely to be used alone but probably either as the initial screening test with a low cut-off, or part of a diagnostic panel.

\subsection*{6.3.2 Other biomarkers}

Adiponectin is an adipokine that is exclusively synthesized by adipose tissue with roles in glucose and lipid metabolism.\textsuperscript{131} Hypoadiponectinemia is associated with NAFLD and NASH.\textsuperscript{132} Nonetheless, the large variations in adiponectin levels observed in different studies make it unsuitable to be the sole diagnostic biomarker in NAFLD/NASH.\textsuperscript{8} Leptin is another potential biomarker which is often studied with adiponectin; a model combining serum suboptimal adiponectin and elevated leptin was used to predicted NASH or borderline NASH.\textsuperscript{133} Nonetheless, conflicting data exist concerning its relationship with NASH or just with morbid obesity independent of liver disease.\textsuperscript{134} Other biomarkers including resistin, ghrelin and retinol binding protein 4 may be appropriate biomarkers of NASH, but are unlikely to serve as diagnostic markers on their own.\textsuperscript{135}
NashTest is made by the same manufacturer as SteatoTest, using patented algorithms combining 13 parameters: age, sex, height, weight, and serum levels of triglycerides, cholesterol, A2M, ApoA1, haptoglobin, GGT, ALT, AST, and total bilirubin. It has modest diagnostic accuracy for NASH (AUROC 0.79) and borderline NASH (AUROC 0.69).\textsuperscript{136} It has poor concordance with histological NAFLD activity score and so cannot be recommended.\textsuperscript{137}

MicroRNAs (miR) are highly conserved, small non-coding RNAs of sizes 18–25 nucleotides which regulate gene expression at the post-transcriptional level.\textsuperscript{138} Each miR can regulate hundreds of target genes. miRs have been increasing recognised in the pathogenesis and diagnosis of NAFLD and NASH.\textsuperscript{139} MicroRNA (miR)-122 and miR-34a levels were higher in NASH group compared with patients with simple steatosis.\textsuperscript{140}

6.4 Noninvasive tests of liver fibrosis (Table 5)

Since fibrosis is the most powerful (and possibly the only independent) prognostic factor for liver-related outcomes in NAFLD, including HCC development and mortality,\textsuperscript{62,141} fibrosis assessment is of paramount clinical importance. Screening for varices and HCC should be offered in case of cirrhosis. Because of the pitfalls of liver biopsy discussed in Section 6.1, noninvasive serological and physical tests have been developed to assess liver fibrosis.

6.4.1 Serum tests

Over the past several decades, panels of tests (often with clinical variables) including NAFLD fibrosis score (NFS), FIB-4, BARD score, enhanced liver fibrosis (ELF) panel, FibroTest, FibroMeter, and Hepascore have shown reasonable diagnostic accuracy (AUCs > 0.8) when
used to assess the extent of liver fibrosis. In addition, some of these tests predict long-term prognoses such as the risk of incident diabetes and overall, cardiovascular-related, and liver-related mortality. However, each of the reported studies appears to have used its own cutoff values, as a result of which no widely accepted cutoff values to separate patients at low and high risk have been defined.

6.4.2 Physical tests

Recent tools to assess liver stiffness include transient elastography (TE), acoustic radiation force impulse (ARFI) elastography, and magnetic resonance elastography (MRE). A recent meta-analysis showed that TE had high sensitivity and specificity when used to identify fibrosis in patients with NAFLD. However, up to 20% of TE examinations yielded unreliable results, especially among patients with high BMI. The use of XL probe can increase the success rate of examination in obese patients, but proper training is required. ARFI elastography has also afforded acceptable accuracy in patients with NAFLD (AUC > 0.8). MRE was the most accurate of the noninvasive physical assessment tools. However, MRE is not widely available and is rarely used in clinical practice because of the high cost.

6.4.3 Investigations in the Asia-Pacific region

Several studies in this region have assessed the cross-sectional accuracy of noninvasive surrogates of liver biopsy among Asian patients with NAFLD. Some have suggested that the combined use of serum tests and physical tools can yield more reliable data than that afforded by either method alone. However, cutoff thresholds remain undefined and as a result, the prognostic implications of various values have not yet been adequately...
investigated. Thus, at the present time, the clinical use of such tools to avoid liver biopsy remains undefined.\textsuperscript{164, 165}

\textbf{6.4.4 Limitations}

A major limitation of noninvasive testing is that most investigations have been performed in studies featuring a cross-sectional design. Thus, the ability of the tests to monitor the natural history of disease, and to predict outcomes or responses to therapeutic intervention remains unclear.

\textbf{6.5 HCC screening}

The annual incidence of developing HCC in NASH cirrhosis is 2.26\%, and the mortality of such cases is 47\% HCC related deaths over 5.3 years.\textsuperscript{70} Cost-effectiveness data from the West suggest that twice yearly ultrasound for HCC surveillance is cost-effective when the risk of developing HCC is >1.5\% per year.\textsuperscript{166} Hence, all NASH patients with cirrhosis should undergo HCC surveillance similar to patients with cirrhosis from other aetiologies.

Ultrasound every 6 months is the most practical screening modality although the sensitivity and specificity of ultrasound in the echogenic fatty liver is not known. This may result in additional need for cross-sectional imaging and affect the cost-utility of surveillance.\textsuperscript{167} The benefit of adding serum AFP remains unclear.\textsuperscript{168}

The issue of HCC occurring in non-cirrhotic livers of patients with NAFLD was considered in Section 3.5. However, the exact risk for each fibrosis stage is unknown, so it is not possible to calculate cost-effectiveness of HCC surveillance for non-cirrhotic patients in the Asian context or elsewhere. The risk of developing HCC in patients with steatosis/
steatosis without advanced fibrosis is probably low with prospective population studies showing that the incidence of HCC being 0.25% HCC after 5.6 years.\textsuperscript{169}

Markers that independently predict increased risk of HCC in non-cirrhotic NASH include \textit{PNPLA3} rs738409 C>G gene polymorphism\textsuperscript{170}, diabetes, obesity, hypertension, cigarette smoking and family history. These factors may potentially select higher risk groups for screening, thereby improving cost-effectiveness. However, as yet there is insufficient modeling or validation data to make any recommendations, and this is an important area for future study.

6.6 Extrahepatic manifestations of NAFLD

Insulin resistance is central to the pathogenesis of both NAFLD and metabolic syndrome. Multiple studies have demonstrated that patients with NAFLD have a higher prevalence of features of metabolic syndrome including obesity, T2DM and hyperlipidemia.\textsuperscript{3, 171, 172} In Asian cohorts, NAFLD independently increases the risk of incident diabetes mellitus by 2 to 5-fold.\textsuperscript{173-176} The combination of diabetes mellitus with NAFLD significantly increases metabolic complications and all-cause mortality.\textsuperscript{177}

Cohort studies of NAFLD patients show that advanced fibrosis (NASH) have an increased mortality from cardiovascular causes.\textsuperscript{146} Several Asian studies have shown that NAFLD is an independent risk factor for coronary atherosclerosis\textsuperscript{178, 179} as well as coronary artery disease\textsuperscript{180-182}. However, the efficacy of screening for NAFLD in patients with coronary artery disease or coronary artery disease in NAFLD patients is yet to be proven.\textsuperscript{183}

NAFLD, especially NASH, is independently associated with a higher prevalence of chronic kidney disease.\textsuperscript{184} Although the strength of this association varies between different cohorts of NAFLD patients, among Asian NAFLD patients defined by ultrasound or raised
liver enzymes, a strong independent association with 1.5 to 2-fold increase in incident adjusted risk has been found consistently.\textsuperscript{182, 185, 186}

Three large Asian studies have reported increased risk of colorectal adenomas in NAFLD patients.\textsuperscript{187-189} In both retrospective and prospective cohorts, the risk of colorectal adenoma and carcinoma in NAFLD patients is up to 1.5 and 3-fold higher respectively compared to patients without NAFLD. These associations appear stronger in NASH patients than among those with simple steatosis. However, no prospective cancer screening trials in NAFLD patients have been performed to support screening beyond the current cancer screening guidelines.

NAFLD is independently associated with obstructive sleep apnoea and osteoporosis. A meta-analysis of 18 studies using polysomnography to define obstructive sleep apnoea found a 2 to 3-fold increased risk of NAFLD including NASH and advanced fibrosis with obstructive sleep apnoea.\textsuperscript{190} Conversely, the risk of obstructive sleep apnoea among NAFLD patients is not known. Korean women with ultrasound-diagnosed NAFLD have been reported to have lower bone mineral density than those without NAFLD\textsuperscript{191}, while the prevalence of osteoporotic fractures in Chinese males was increased among those with NAFLD.\textsuperscript{192}

Recommendation Statements

6.1 Liver biopsy should be performed in NAFLD patients whose diagnosis is unclear, or where there is a suspected possibility of co-existing chronic liver diseases. (B1)

6.2 The NAFLD Activity Score was designed to document histological changes over time in clinical studies and should not be used as a diagnostic tool. In contrast, the FLIP algorithm
was designed to diagnose NASH. Data on their performance in the Asia-Pacific population are scarce. (B2)

6.3 CAP by FibroScan or MR-based techniques are accurate alternatives to abdominal ultrasonography for the detection of steatosis, by virtue of their higher sensitivity. However, their applicability depends on the availability and local cost of the modality. (B1)

6.4 Prediction models for NAFLD may be used in epidemiological studies. Their application at the individual patient level is unclear. (B2)

6.5 Biomarkers for NASH are not yet ready to replace liver biopsy as a reliable diagnostic tool. (B2)

6.6 Biomarkers for NASH, with cut-off values of high sensitivity, may be used as the initial screening strategy to reduce the need for liver biopsy. Further research is needed to develop better biomarkers or diagnostic algorithms. (B2)

6.7 Noninvasive serum and physical tests afford modest but possibly acceptable accuracies when used to measure the fibrotic burden in patients with NAFLD. (A2)

6.8 Appropriate cut-off values for identifying patients who are at low and high risk of developing liver-related complications are required. Also, the prognostic performance of noninvasive tests used for monitoring changes in the fibrotic burden requires further validation. (C2)

6.9 Liver biopsy should be considered when assessment of liver fibrosis using noninvasive tests is inconclusive. (B1)

6.10 Patients with NASH cirrhosis are at increased risk of developing hepatocellular carcinoma and should undergo regular surveillance with ultrasound examination every 6 months. (A1)

6.11 The role of serum AFP is yet to be evaluated in NASH- HCC. (C2)
6.12 Although HCC can occur in non-cirrhotic NASH patients, the overall risk is low, especially for those with simple steatosis. At present, no recommendations for screening can be made. (B2)

6.13 NAFLD is associated with increased risk of cardiovascular disease, chronic kidney disease and colorectal neoplasm. Other possible associations include obstructive sleep apnoea and osteoporosis. However, there is insufficient prospective data available to support screening patients with these associated disorders. Risk assessment for patients with such conditions should be individualized. (B1)

6.14 There is a need to define Asian patients with NAFLD who are at the greatest risk of developing metabolic complications and for whom, cost effective interventional therapies can be tested. (C1)

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Table 1. Grading of evidence and recommendations (adapted from the GRADE system)\(^2\)

<table>
<thead>
<tr>
<th>Grading of evidence</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>High quality evidence from meta-analysis or randomized controlled trials without major limitations; or in the case of non-interventional studies, evidence from high quality observational studies. Further research is unlikely to change our confidence in the estimate of effect.</td>
</tr>
<tr>
<td>B</td>
<td>Moderate quality evidence from meta-analysis or randomized controlled trials with obvious limitations or observational studies. Further research is likely to have an important impact on our confidence in the estimate of effect.</td>
</tr>
<tr>
<td>C</td>
<td>Low or very low quality evidence from randomized controlled trials or observational studies with major limitations; case series and case reports. Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any estimate of effect is uncertain.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grading of recommendations</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Strong recommendation based on the quality of evidence, presumed patient-important outcomes, and costs.</td>
</tr>
<tr>
<td>2</td>
<td>Weaker recommendation because of variability in preferences and values, uncertainty, and higher cost or resource consumption.</td>
</tr>
</tbody>
</table>
Table 2. Risk factors for NAFLD

1. NAFLD
   - Overnutrition (invariable)
   - Insulin resistance (invariable with NASH)
   - Gut microbiota (mainly experimental data)
   - Genetic variations in addition to family history of T2DM, cirrhosis and fatty liver disease:
     - PNPLA3, TM6SF2, LEPR, PPAR, SREBP, MTTP, positions −308 or −238
     - of TNF-α, MnSOD, MBOAT7, TMC4, FDFT1*

2. Fatty liver attributable to causes other than alcohol or over-nutrition ("secondary
   NAFLD")**
   - Medications
     - valproic acid, estrogens, tamoxifen, corticosteroids, tetracycline,
     - amiodarone, perhexiline maleate, methotrexate,
     - 4,4'-diethylaminoethoxyhexesterol, chloroquine, calcium channel blockers, L-asparaginase
   - Occupational exposure to hepatotoxins
   - Malnutrition (especially Kwashiokor)
   - Total parenteral nutrition, rapid weight loss
   - Surgically altered bowel anatomy:
     - jejunoileal bypass, jejunocolic bypass, gastroplasty, extensive small-bowel resection
   - Polycystic ovary syndrome
   - Wilson’s disease
   - Weber Christian disease
   - Severe insulin resistance with lipodystrophies

*45, 46
**25, 37

Table 3. Wilson and Jungner classic screening criteria.85

1. The condition sought should be an important health problem.

2. There should be an accepted treatment for patients with recognized disease.

3. Facilities for diagnosis and treatment should be available.

4. There should be a recognizable latent or early symptomatic stage.

5. There should be a suitable test or examination.

6. The test should be acceptable to the population.

7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.

8. There should be an agreed policy on whom to treat as patients.

9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.

10. Case-finding should be a continuing process and not a “once and for all” project.
<table>
<thead>
<tr>
<th>Modalities</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Diagnostic Performance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prediction models</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatty liver index [Bedogni]</td>
<td>Common clinical and laboratory parameters</td>
<td>Complex formula</td>
<td>AUROC: 0.84</td>
</tr>
<tr>
<td></td>
<td>High applicability</td>
<td>Modest accuracy</td>
<td>Cut-off: 30 60</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sensitivity (%): 87 64</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Specificity (%): 64 86</td>
</tr>
<tr>
<td>NAFLD liver fat score [Kotronen]</td>
<td>Common clinical and laboratory parameters</td>
<td>Complex formula</td>
<td>AUROC: 0.86-0.87</td>
</tr>
<tr>
<td></td>
<td>High applicability</td>
<td>Modest accuracy</td>
<td>Cut-off: -0.640</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sensitivity (%): 86</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Specificity (%): 71</td>
</tr>
<tr>
<td>SteatoTest [Poynard05]</td>
<td>High sensitivity and negative predictive value even with mild steatosis (&gt; 5%)</td>
<td>Some uncommon laboratory parameters involved</td>
<td>AUROC: 0.72-0.86</td>
</tr>
<tr>
<td></td>
<td>High applicability</td>
<td>High cost</td>
<td>Cut-off: 0.30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Modest specificity</td>
<td>Sensitivity (%): 90</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Specificity (%): 54</td>
</tr>
<tr>
<td>Abdominal ultrasonography</td>
<td>Inexpensive</td>
<td>Sensitivity decreased with morbid obesity</td>
<td>AUROC: N.A.</td>
</tr>
<tr>
<td></td>
<td>Widely available,</td>
<td>Operator dependent</td>
<td>Cut-off: N.A.</td>
</tr>
<tr>
<td></td>
<td>Can be used as a screening tool</td>
<td>Cannot detect subtle changes</td>
<td>Sensitivity (%): 91</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Specificity (%): 89</td>
</tr>
<tr>
<td>Controlled attenuation parameter</td>
<td>High sensitivity even with mild steatosis (&gt;10%)</td>
<td>No consensus in cut-off</td>
<td>AUROC: S1: 0.80 to 0.91</td>
</tr>
<tr>
<td>[Wong WJH13]</td>
<td>Instant results</td>
<td>Sensitive but not as specific</td>
<td>Cut-off: 215-283 dB/m</td>
</tr>
<tr>
<td></td>
<td>Inexpensive</td>
<td></td>
<td>Sensitivity (%): 76-91%</td>
</tr>
<tr>
<td></td>
<td>Can grade steatosis</td>
<td></td>
<td>Specificity (%): 79-81%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>S2: 0.81 to 0.95</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cut-off: 252-259 dB/m</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sensitivity (%): 89</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Specificity (%): 86</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>S3: 0.66 to 0.93</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cut-off: 292-296 dB/m</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sensitivity (%): 100%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Specificity (%): 78%</td>
</tr>
<tr>
<td>H\textsuperscript{3}-MRS [Szczepaniak]</td>
<td>High sensitivity even with mild steatosis (&gt;5-10%)</td>
<td>Limited availability</td>
<td>AUROC: N.A.</td>
</tr>
<tr>
<td></td>
<td>High cost</td>
<td></td>
<td>Cut-off: 55.6 mg/g</td>
</tr>
<tr>
<td></td>
<td>Need on patients</td>
<td></td>
<td>Sensitivity (%): N.A.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Specificity (%): N.A.</td>
</tr>
</tbody>
</table>
Hepatic steatosis: $S_1 \geq 11\%$; $S_2 \geq 34\%$; $S_3 \geq 67\%$.

$^1$H-MRS: Proton magnetic resonance spectroscopy; MRI-PDFF = magnetic resonance imaging - estimated proton density fat fraction; N.A. = not available.
Table 5. Comparison of different tests for NAFLD to assess the degree of liver fibrosis

<table>
<thead>
<tr>
<th>Tests</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum tests</td>
<td>Good reproducibility</td>
<td>Not specific for liver</td>
</tr>
<tr>
<td></td>
<td>High applicability, readily available</td>
<td>Not immediate result acquisition</td>
</tr>
<tr>
<td></td>
<td>No additional cost, if not patented</td>
<td>High cost and limited availability, if patented</td>
</tr>
<tr>
<td></td>
<td>Acceptable accuracy to exclude advanced fibrosis and cirrhosis</td>
<td>Inappropriate to discriminate between intermediate stages of fibrosis</td>
</tr>
<tr>
<td></td>
<td>Has prognostic value</td>
<td></td>
</tr>
<tr>
<td>Physical tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transient elastography</td>
<td>Specific for liver - check pure physical property</td>
<td>Needs a high-cost tool</td>
</tr>
<tr>
<td>Short learning curve</td>
<td>Reliabale results only 75% in obese subjects despite of XL probe</td>
<td></td>
</tr>
<tr>
<td>Fast acquisition</td>
<td>False positivity with high ALT, ascites, cholestasis, and heart failure</td>
<td></td>
</tr>
<tr>
<td>Immediate results</td>
<td>Inappropriate to discriminate between intermediate stages of fibrosis</td>
<td></td>
</tr>
<tr>
<td>Good reproducibility</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Accepted Article</strong></td>
<td><strong>Low intra- and inter-observer variability</strong></td>
<td><strong>Good performance to exclude advanced fibrosis and cirrhosis</strong></td>
</tr>
<tr>
<td>---------------------</td>
<td>---------------------------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Has prognostic value</td>
</tr>
<tr>
<td><strong>ARFI elastography</strong></td>
<td>Specific for liver - check pure physical property</td>
<td>Needs a high-cost tool</td>
</tr>
<tr>
<td></td>
<td>Fast acquisition</td>
<td>Limited data</td>
</tr>
<tr>
<td></td>
<td>Immediate results</td>
<td>Narrow range</td>
</tr>
<tr>
<td></td>
<td>Simultaneous acquisition of hepatic and tumor information</td>
<td>Smaller ROI than transient elastography</td>
</tr>
<tr>
<td></td>
<td>Good performance to exclude advanced fibrosis and cirrhosis</td>
<td>No quality criteria</td>
</tr>
<tr>
<td></td>
<td>Inappropriate to discriminate between intermediate stages of fibrosis</td>
<td></td>
</tr>
<tr>
<td><strong>Shear wave elastography</strong></td>
<td>Specific for liver - check pure physical property</td>
<td>Needs a high-cost tool</td>
</tr>
<tr>
<td></td>
<td>High intra-observer reliability</td>
<td>Limited data</td>
</tr>
<tr>
<td></td>
<td>Fast acquisition</td>
<td>~15% of failure rates</td>
</tr>
<tr>
<td></td>
<td>Immediate results</td>
<td>No quality criteria</td>
</tr>
<tr>
<td></td>
<td>Simultaneous acquisition of hepatic and tumor information</td>
<td>Inappropriate to discriminate between intermediate stages of fibrosis</td>
</tr>
<tr>
<td>Good performance to exclude advanced fibrosis and cirrhosis</td>
<td>Reliable results only in 73% of patients with BMI $\geq 30$ kg/m$^2$</td>
<td></td>
</tr>
<tr>
<td>MRE</td>
<td>Specific for liver - check pure physical property</td>
<td>Needs a high-cost tool</td>
</tr>
<tr>
<td>Estimation of the entire liver</td>
<td>Limited data</td>
<td></td>
</tr>
<tr>
<td>Not affected by obesity</td>
<td>Not immediate result acquisition</td>
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</tr>
<tr>
<td>Simultaneous acquisition of hepatic and tumor information</td>
<td>Needs a specific facility</td>
<td></td>
</tr>
<tr>
<td>Simultaneous MRS for steatosis</td>
<td>High cost</td>
<td></td>
</tr>
<tr>
<td>Probably more accurate than transient elastography</td>
<td>Time-consuming</td>
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<tr>
<td></td>
<td></td>
<td>Inaccurate in iron overload</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cannot be used in patients with implantable devices</td>
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</tbody>
</table>

NAFLD, nonalcoholic fatty liver disease; ALT, alanine aminotransferase; ARFI, acoustic radiation force impulse; ROI, region of interest; MRS, magnetic resonance spectroscopy.
The Asia-Pacific Working Party on Nonalcoholic Fatty Liver Disease Guidelines 2017
Part 2: Management and special groups

Shiv Chitturi¹, Vincent Wai-Sun Wong²,³, Wah-Kheong Chan⁴, Grace Lai-Hung Wong²,³, Simon Kin-Hung Wong⁵, Jose Sollano⁶, Yen-Hsuan Ni⁷, Chun-Jen Liu⁸, Yu-Cheng Lin⁷, Laurentius Adrianto Lesmana⁹, Seung Up Kim¹⁰, Etsuko Hashimoto¹¹, Masahide Hamaguchi¹², Khean-Lee Goh⁴, Jiangao Fan¹³, Ajay Duseja¹⁴, Yock Young Dan¹⁵, Yogesh Chawla¹⁴, Geoff Farrell¹, Henry Lik-Yuen Chan²,³

¹Gastroenterology and Hepatology Unit, The Canberra hospital, Canberra, Australia
²Department of Medicine and Therapeutics, ³State Key Laboratory of Digestive Disease, and
⁵Department of Surgery, The Chinese University of Hong Kong, Hong Kong, China
⁴Department of Medicine, University of Malaya, Kuala Lumpur, Malaysia
⁶University of Santo Tomas, España Boulevard, Manila, the Philippines
⁷Hepatitis Research Center, National Taiwan University, Taipei, Taiwan
⁸Department of Internal Medicine, Hepatitis Research Center and Graduate Institute of
Clinical Medicine, National Taiwan University College of Medicine and Hospital
⁹Digestive Disease and GI Oncology Centre, Medistra Hospital, Jakarta, Indonesia
¹⁰Department of Internal Medicine, Institute of Gastroenterology, Yonsei University Collge of
Medicine, Seoul, Korea
¹¹Department of Internal Medicine and Gastroenterology, Tokyo Women’s Medical University,
Tokyo, Japan
¹²Department of Diabetology, Kameoka Municipal Hospital, Kameoka, Japan
¹³Xin Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai,
China
¹⁴Department of Hepatology, Post Graduate Institute of Medical Education and Research,
Chandigarh, India
¹⁵Department of Medicine, Yong Loo Lin School of Medicine, National University of
Singapore, Singapore
Correspondence:
Prof Geoffrey C. Farrell
The Canberra Hospital, PO Box 11, Woden, ACT 2606, Australia
Tel: 61-2-6244-2473 Fax: 61-2-6244-3235
E-mail: geoff.farrell@anu.edu.au

Dr Vincent Wong
Department of Medicine and Therapeutics, 9/F, Clinical Sciences Building, Prince of Wales Hospital, 30-32 Ngan Shing Street, Shatin, Hong Kong
Tel: 852-26321205 Fax: 852-26373852
E-mail: wongv@cuhk.edu.hk

Conflict of interests:
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Yock Young Dan served as an advisory board member and has received research grants from AbbVie, Bristol-Myers Squibb and Gilead Sciences.
Khean-Lee Goh served as an advisory board member of Gilead Sciences; and a speaker for AbbVie and Gilead Sciences.
Grace Wong has served as an advisory committee member for Otsuka and Gilead. She has also served as a speaker for Abbott, Abbvie, Bristol-Myers Squibb, Echosens, Furui, Gilead, Janssen, Otsuka and Roche.
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7. Management

7.1 How to assess efficacy of interventions

In clinical practice, and particularly among those who appear to have mild liver disease, it may be sufficient to note changes (normalisation) of liver tests and serum lipids/blood glucose in relation to lifestyle intervention and weight reduction. However, this is not sufficient for clinical trials because: (1) liver pathology is not defined unless biopsy is performed, and (2) the only legitimate surrogate marker for an improved clinical outcome of liver disease is improvement in liver fibrosis.

Towards the latter goal, reversal of NASH pathology at present seems most useful as the change most likely to prevent fibrosis progression or reversal, noting that reversal of liver fibrosis with resolution of NASH has now been clearly documented in weight reduction studies. The most robust endpoint for studies of NASH with liver fibrosis but not cirrhosis would be the reversal of NASH and improvement of fibrosis either by fibrosis score on semi-quantitative measurements of collagen density. This recommendation accords with recent recommendations of a United States of America FDA and AASLD Joint Working Party and is already being introduced post-hoc into major on-going studies of new drug treatments for NASH.

At present, an endpoint for trials of NASH with cirrhosis is more difficult to define as cirrhosis reversal may not occur, and longer term clinical outcomes or surrogate measures of these (e.g. reduction in wedged hepatic vein pressure) is ideally required.

The NAFLD Activity Score (NAS) is relatively uninformative in several large studies. Several studies have also shown that it is inappropriate to diagnose NASH based on NAS because significant weighting (3 out of 8 points) is given to the degree of hepatic steatosis. Improvement or reversal of steatosis has not been shown to correlate well with reversal of

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NASH or liver fibrosis. Improvement in NAS also does not weigh the fibrosis component, and the addition of “failure to worsen fibrosis score” may be not be a satisfactory cut-off for a disease-intervening treatment. Besides, NAS does not correlate well with long-term clinical outcomes, particularly after adjustment for fibrosis stage. Therefore, “resolution of NASH without worsening in fibrosis” and “fibrosis improvement without worsening of NASH” are now used in phase 3 studies as primary endpoints.

The utility of surrogate (non-invasive) markers as primary endpoints of phase 1 or phase 2A studies in NASH is controversial. A hope is that biomarker and physical indicators of inflammatory severity and fibrosis may substitute liver biopsy to facilitate conduct of such studies, but at present the evidence allowing this is not sufficiently robust to either “rule in” or “rule out” pharmacological agents before proceeding to larger scale studies. On the other hand, use of physical markers of liver steatosis (which actually determine hepatic triglyceride content) such as MR spectroscopy may be flawed for a liver disease (NASH) whose greatest clinical importance relates to fibrosis and possibly liver cell injury and liver inflammation. This working party does not accept MRI as a substitute for liver biopsy in NASH studies. On the other hand, while non-invasive tests of fibrosis such as transient elastography have been extensively evaluated in cross-sectional studies of NAFLD patients, their role as a monitoring tool should be further explored in longitudinal studies.

7.2 Lifestyle management

7.2.1 Diet and exercise programs

Several studies have evaluated lifestyle changes (diet, physical activity) in managing NAFLD. Initial studies correlated histologic improvement with a 7% reduction in body weight. Exercise can independently improve hepatic steatosis without weight loss but

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weight loss is usually required for NASH resolution. A key Cuban lifestyle management program (n=293) showed a clear dose-response between weight loss and improvement in liver histology; 58% of those achieving >5% and 90% of those achieving weight loss of >10%, respectively showed resolution of NASH. Only the latter showed improvement in fibrosis stage (in 45%).

A systematic review published in 2012 (23 studies, including 7 randomized and 6 controlled trials) had already noted the importance of lifestyle intervention strategies. The included trials differed in design, with some involving diet (n=11) or exercise alone (n=2), but the majority (n=19) combined both modalities. There was a trend towards reduced inflammatory activity in 5 studies, with 2 showing statistical significance. Data on fibrosis reduction were seen only in 1 study. Combined diet/exercise strategies are more effective in reducing liver fat than either modality alone (49.8% vs. 30.2%, respectively). Asian data support a 10% weight reduction target although some individuals (up to 40%) can improve with lesser degrees (3% to 5%) of weight loss. There are no Asian data supporting NASH resolution through lifestyle changes, and this is a priority for future research.

### 7.2.2 Dietary considerations

Individuals with NAFLD tend to consume energy dense foods, rich in saturated fat, cholesterol and sugar-sweetened beverages but deficient in micronutrients found in fresh fruit, fibre and green vegetables, and omega-3-polyunsaturated fatty acids. Therefore, dietary plans should address these imbalances which are important in preventing/managing co-existing metabolic and cardiovascular disease. However, omega-3-PUFA supplementation has not shown to be beneficial in improving NASH. The aim should be for gradual weight loss (up to 1 kg/week) with a hypocaloric diet (500-1,000 kcal deficit)
because crash diets can worsen NASH. Several different diet protocols have been proposed (low carbohydrate, low fat, Mediterranean diet).\textsuperscript{12} While there are short-term differences with respect to weight loss and reduction in steatosis, these differences are no longer significant with longer follow-up.\textsuperscript{13} Very low calorie diets are unsustainable and are used mainly in preparation for bariatric surgery. Finally, there are no data to support any specific diet with respect to the resolution of NASH.

\textbf{7.2.3 Exercise considerations}

The intensity, volume, and type of exercise required are debated. Ischaemic heart disease is the leading cause of death in NAFLD.\textsuperscript{14, 15} For the general population, physical activity guidelines recommend 30 minutes/day of \textit{moderate-intensity} exercise for $\geq 5$ days/week or a total of $\geq 150$ minutes of per week or \textit{vigorous-intensity} exercise for $\geq 20$ minutes/day on $\geq 3$ days/week ($\geq 75$ minutes/week).\textsuperscript{16} Resistance exercise on 2-3 days/week and flexibility exercises > 2 days/week are also recommended. Only limited data on exercise intensity are available with respect to patients with NASH. In one U.S study based on self-reported physical activity, only vigorous activity (75 min/week) was associated with a reduced likelihood of having NASH (OR 0.65, 95\% CI 0.45-0.98) or advanced fibrosis (OR 0.53, 95\% CI 0.29-0.97).\textsuperscript{17} A Japanese study found a dose-response relationship between exercise volume and reduction in liver fat, with greater response in subjects exercising over 250 minutes/week as compared with those exercising for less than 150 minutes/week.\textsuperscript{18} Resistance and aerobic exercise training have similar effects on hepatic steatosis\textsuperscript{19}, but one systematic review concluded that the former involved lesser energy consumption and therefore could be offered for patients unable to undertake aerobic training.\textsuperscript{20}
High intensity interval training can also reduce hepatic fat but like all other exercise regimes has not independently been shown to improve NASH.\textsuperscript{21}

### 7.2.4 Special considerations in patients with NAFLD

Patients with NAFLD are often sedentary with low levels of cardiorespiratory fitness\textsuperscript{22} and motivation. One U.S study found that nearly a third of their patients were uninterested in making weight-related behavioural changes\textsuperscript{23} and only 20% achieved a weight loss of 5% over an 18-month period.\textsuperscript{24} Therefore, multidisciplinary management with a dietician, psychologist and exercise trainer is needed to achieve desired goals.\textsuperscript{25}

### 7.3 Pharmacological treatment

Although lifestyle management is effective and should be encouraged, not all patients can adhere to diet and exercise. Besides, it is difficult for patients with morbid obesity and musculoskeletal disorders to do sufficient exercise. Therefore, pharmacological treatment may be required in some patients. As illustrated in previous sections, patients with simple steatosis run a benign course and have a low risk of liver-related complications. We should therefore target patients with NASH and/or liver fibrosis.\textsuperscript{26} At present, no drug has been approved by the US Food and Drug Administration or the European Medicines Agency for the treatment of NASH. However, some agents have entered phase 3 development. Besides, a number of agents with indications for other medical conditions have also been tested in NASH patients. Nonetheless, it is important to note that Asian patients are underrepresented in NASH trials, and the data discussed in this section are mostly from international trials with the majority of patients being Caucasians. In addition, the available clinical trials typically apply extensive exclusion criteria and have limited generalizability. For

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instance, the safety and efficacy of the drugs in cirrhotic patients are largely unknown. Table 1 summarizes the agents discussed in this section.

### 7.3.1 Vitamin E

Oxidative stress is considered to be a key mechanism of hepatocellular injury and disease progression in NASH patients. Vitamin E is an anti-oxidant and has been investigated to treat NASH. In the PIVENS trial, vitamin E at a dose of 800 IU/day of α-tocopherol for 96 weeks is associated with a decrease in serum aminotransferases, and histologic improvement in steatosis, inflammation, and ballooning and resolution of steatohepatitis in adults with NASH. In a randomized, vitamin E-controlled trial of bicyclol plus metformin in Chinese patients with NAFLD and impaired fasting glucose, vitamin E at a dose of 300 mg/day for 24 weeks is not better than bicyclol in the improvement of serum aminotransferase and in hepatic histological changes. However, vitamin E has no effect on hepatic fibrosis, insulin resistance, and serum low density lipoprotein cholesterol level. Individuals with resolution of NASH may still be at increased risk of T2DM and cardiovascular disease. In addition, concerns about long-term safety of vitamin E exist, mainly an increase in all-cause mortality, in haemorrhagic stroke and prostate cancer in relatively healthy males older than 50.

### 7.3.2 Thiazolidinediones and other PPAR agonists

Ligands (α, δ, γ) of peroxisome-proliferator activated receptors (“PPAR”) improve insulin sensitivity, hepatic fatty acid oxidation, and have anti-inflammatory effects. Trials with fibrates (clofibrates), which are PPAR-α agonists (clofibrate), have been disappointing but they remain useful in managing hypertriglyceridemia.
A 2011 meta-analysis of 7 randomized trials involving PPAR-\(\gamma\) agonists (thiazolidinediones) showed significant reduction in hepatic steatosis (RR 2.0, CI 1.57-2.6), lobular inflammation (RR 1.7, CI 1.3-2.2) and hepatocellular ballooning (RR 1.6, CI 1.15-2.3), with no or modest effects on fibrosis (RR 1.38, CI 1.01-1.89).\(^{34}\) Some trials have excluded high-risk patients (T2DM or cirrhosis), and pioglitazone appears to work as well in non-diabetic patients.\(^{35}\) A recent trial tried to address this limitation by including patients with pre-diabetes or T2DM but still included only 10% to 14% with advanced liver fibrosis. The overall NASH resolution rate was 51%.\(^{36}\) Resolution of NASH tends to be mainly in the first year\(^{37}\) but continued use is necessary to maintain histologic improvement.\(^{38}\) Adverse effects include weight gain (mean, 4.4 kg) and other safety concerns including myocardial infarction (rosiglitazone) and increased fracture risk, congestive cardiac failure and bladder cancer (pioglitazone).\(^{39}-^{41}\)

**Dual PPAR-\(\alpha\), \(\delta\) agonist** elafibranor (a) was evaluated in a phase IIb randomized controlled trial.\(^{42}\) Patients with NASH (n =276) received 80 mg or 120 mg of elafibranor or placebo for 52 weeks. The primary endpoint of NASH resolution without worsening of fibrosis was not achieved (21%, 23% and 17%, respectively; p = NS) but a post-hoc modified endpoint (no hepatocyte ballooning and no/mild lobular inflammation without fibrosis progression) was observed in 19%, 13% and 12%, respectively (p= 0.045). There were favourable effects on the lipid profile, lack of weight gain but a mild reversible creatinine increase was seen in 4%.

Asian data on the use of PPAR agonists are scarce. In one Indian study, pioglitazone appears to have better metabolic and histological benefits than pentoxifylline.\(^{43}\)
7.3.3 Pentoxifylline

Pentoxifylline is a phosphodiesterase inhibitor with antioxidant properties, and was originally proposed to inhibit tumor necrosis factor-alpha (TNFα) production. Improvement in steatohepatitis was documented in methionine-choline deficient and high fat diet-induced models of NASH, even in the absence of any change in serum or hepatic TNF.44 Pilot, non-randomized studies in human NASH also showed improvement in serum aminotransferases and histology, but again without impact on serum TNF.45 A subsequent randomized controlled trial (RCT) showed no significant histologic differences between the treatment and control groups.46 In another RCT, pentoxifylline failed to reduce hepatocyte ballooning yet achieved statistically but not clinically significant reduction in fibrosis (-0.2 vs. +0.4 fibrosis stage among those on pentoxifylline vs. placebo).47 There are also safety concerns about pentoxifylline as some adverse events were noted in previous trials in alcoholic hepatitis (e.g. gastrointestinal upset, infection, etc). Therefore, pentoxifylline cannot be recommended.

7.3.4 Metformin

Since insulin resistance plays a central role in the pathogenesis of nonalcoholic fatty liver disease (NAFLD), insulin sensitizing drugs including metformin have been used in the treatment of patients with NAFLD. After its usefulness in reversing fatty liver was shown in leptin-deficient ob/ob mice, metformin was first used in humans in a pilot study of 20 patients with NASH and in comparison to six controls was shown to improve hepatic transaminases, insulin sensitivity and liver volume.48,49 Thereafter, several other studies, including one from Asia, have shown its utility in improving serum biochemistry and insulin resistance, but the randomised data showing histological improvement with metformin is

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sparse.\textsuperscript{50-53} One of the first randomized trials in which metformin (2g/day) given for 12 months was compared with vitamin E or weight reducing diet, showed it to be effective in improving the aminotransferase levels and histological reduction in liver fat, necroinflammation, and fibrosis in a small number of liver biopsies done only in the metformin group.\textsuperscript{54} Another randomized, placebo controlled study which used metformin (2.5-3g/day) for 6 months did not show any difference in CT or histologically assessed steatosis, NAS-score, liver transaminases or insulin resistance in comparison to controls.\textsuperscript{55} Similarly, in another placebo controlled trial, even though metformin improved insulin resistance, it failed to improve the liver histology.\textsuperscript{56} Even though mild gastrointestinal disturbances have been reported, none of the studies using metformin reported any major side effects like hypoglycemia or lactic acidosis.\textsuperscript{54-56} Metformin is safe and appears to reduce the risk of HCC in animal and observational studies.\textsuperscript{57, 58} On the other hand, as shown in several meta-analyses, metformin does not reduce liver fat or improve liver histology and therefore cannot be recommended as a primary treatment for NAFLD/NASH.\textsuperscript{59-61}

### 7.3.5. **Glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors**

Glucagon-like peptide-1 (GLP-1) agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors are newer drugs to treat T2DM by modulating beta cell responsiveness. The GLP-1 agonist liraglutide has also been registered for the treatment of obesity and overweight with weight-related conditions. GLP-1 is secreted by intestinal L cells in response to nutrients, and acts as an incretin by increasing insulin secretion and decreasing glucagon secretion. It suppresses appetite centrally and delays gastric emptying, the latter further contributing to reduced food intake. DDP-4 catalyzes the degradation of circulating incretins. DPP-4 inhibitors thus exert metabolic effects by raising serum incretin levels.
One randomized controlled trial (the LEAN study) tested the use of liraglutide in NASH patients for 48 weeks using histological endpoints. Resolution of definite NASH was achieved in 9 of 23 (39%) patients who received liraglutide and 2 of 22 (9%) in those who received a placebo (P=0.019). Although the proportion of patients with improvement in fibrosis was similar, fewer patients in the liraglutide group had fibrosis progression (2/23 (9%) versus 8/22 (36%); P=0.04). In a related mechanistic substudy, liraglutide improved insulin sensitivity in both liver and adipose tissue, and reduced fasting hepatic de novo lipogenesis. Liraglutide is associated with gastrointestinal upset, and may partly exert beneficial effects on NAFLD by causing weight reduction. Recently, liraglutide has also been shown to reduce cardiovascular deaths, myocardial infarction and stroke in diabetic patients (hazard ratio 0.87). All GLP-1 agonists are given as injections. Although there has been no study on Asian NASH patients, the pharmacokinetics of GLP-1 agonists do not appear to differ between Asian and non-Asian patients. GLP-1 agonists also appear to reduce glycated hemoglobin more effectively in Asian patients with T2DM.

In contrast, DDP-4 inhibitors do not seem to reduce weight. There are conflicting data on their effect on hepatic steatosis based on radiological assessment. Furthermore, histological data are lacking.

7.3.6. Obeticholic acid

Obeticholic acid is a potent agonist of the farnesoid X receptor, which is responsible for not only bile acid but also glucose and lipid metabolism. It has been approved by the US Food and Drug Administration for the treatment of primary biliary cholangitis. In the phase 2 FLINT study in patients with biopsy-proven NASH, a histological response of reduction in the NAFLD activity score by 2 points or more with no worsening of fibrosis was achieved in 45%
of patients receiving obeticholic acid and 21% of those receiving placebo for 72 weeks.\textsuperscript{70} Patients receiving obeticholic acid were also more likely to have improvement in fibrosis (35% versus 19%). In another phase 2 trial in Japanese NASH patients, obeticholic acid only increased the proportion of patients achieving the same histological endpoint as in the FLINT study when it was given at a very high dose of 40 mg daily, which will likely be limited by side effects (only top line results announced). Pruritus is a common side effect of obeticholic acid. The drug also causes an atherogenic lipid profile with high total cholesterol and low density lipoprotein-cholesterol, as well as reduced high density lipoprotein-cholesterol. The impact on cardiovascular outcome should be clarified. The REGENERATE study (ClinicalTrials.gov Identifier NCT02548351) is an ongoing phase 3 study testing obeticholic acid in NASH patients.

\subsection*{7.3.7 Omega-3 fatty acid}
A systematic review concluded that omega-3 polyunsaturated fatty acids (n-3 PUFAs) supplementation may reduce liver fat at a dose of \( \geq 0.83 \text{ g/day} \).\textsuperscript{71} However, no significant improvement was seen on liver function tests. A recent meta-analysis supports the use of n-3 PUFAs because it may lower liver enzyme (gamma-glutamyltransferase [GGT]) and blood lipid levels (tryglycerides and high-density lipoprotein (HDL) cholesterol).\textsuperscript{72} Studies addressing liver histology outcome did not find histology improvement in NASH patients supplemented with low- (1,800 mg/day) or high-dose (>2,700 mg/day) n-3 PUFA.\textsuperscript{11,73} NASH patients with diabetes also failed to show histology improvement after PUFA supplementation.\textsuperscript{74}
The optimal duration of supplementation and most effective dose of n-3 PUFA have not been determined. It also remains unclear what the optimal source of n-3 PUFA is, in terms of whole foods, i.e. fish oil or purified product. One study used purified docosahexaenoic acid (DHA) plus eicosapentaenoic acid (EPA) at a dose of 4 g/day and demonstrated a reduction of liver fat assessed by magnetic resonance spectroscopy (“MRS”).75 There was no report on the adverse effects of n-3 PUFA supplementation.

7.3.8 Liver supplements

Silymarin may be useful for the treatment of NASH but the optimal dose and duration requires further studies.

Silymarin, which is derived from the milk thistle plant *Silybum marianum*, is a complex mixture of 6 major flavonolignans (silybins A and B, isosilybins A and B, silychristin, and silydianin), as well as other minor polyphenolic compounds.76 Several clinical trials have suggested that silymarin may be useful for the treatment of NAFLD.77-82 In a randomized, double-blinded, placebo-controlled study on patients with biopsy-proven NASH, silymarin dosage of 700 mg three times daily for 48 weeks resulted in significantly higher percentage of fibrosis reduction compared with placebo (22.4% vs. 6.0%, p = 0.023).83 The dosage of 700 mg three times daily was safe and well-tolerated, consistent with that reported previously and was chosen to provide the highest likelihood of finding a therapeutic effect in the study. Silymarin may also have beneficial effects on other components of the metabolic syndrome.84-86
7.4 The use of statins in NAFLD patients

A systematic review has described the relative safety of statin use, i.e., liver failure notification rate to regulatory authorities of 1/million person-years and, fewer hepatobiliary adverse events with statins compared to placebo in randomized controlled trials (RCTs) involving patients with liver disease.\(^\text{87}\) A recent Cochrane review, which included two RCTs with small patient populations and a high risk of bias, showed statins improved transaminase levels and sonographic findings, but liver-related morbidity and mortality were not reported. Despite the low quality of the evidence, this review concluded that statin use in NAFLD may be justified because they may prevent the adverse outcomes of conditions related to NASH.\(^\text{88, 89}\) A more recent review underlines the safety of statin use in patients with NAFLD including those with slightly elevated alanine transaminases, i.e., <3x ULN and, their value in reducing the associated cardiovascular morbidity in this population.\(^\text{90}\) Experts have recommended that mild to modest increases in liver enzymes are not contraindications to either initiating or continuing statin use in other chronic liver diseases, such as uncomplicated chronic hepatitis B and C, or in compensated liver cirrhosis. There are fragmentary data that statin use may reduce risk of HCC (among other malignancies), but this aspect requires further directed study. However, routine prescription of a statin is not recommended in patients with decompensated cirrhosis and acute liver failure.\(^\text{91-95}\)

7.5 Bariatric surgery

NAFLD often accompanies obesity and its complications, including type 2 diabetes, obstructive sleep apnoea, gastroesophageal reflux disease and metabolic syndrome. Weight loss can be a highly effective intervention for some of these diseases. Thus, bariatric surgery is currently the recommended treatment in T2DM patients with class II and class III
obesity. The International Federation of Surgery for Obesity ("IFSO") Asia-pacific Chapter had published a consensus statement in 2011 that Asian patients should consider bariatric surgery among their treatment options for metabolic syndrome and T2DM if their BMI >30kg/m². 

Although there is a lack of randomized controlled trials comparing the effects of bariatric surgery with any other interventions on NAFLD or NASH, several retrospective and prospective observational cohort studies have demonstrated bariatric surgery often improves and even completely resolves NASH. In recent systemic reviews and meta-analyses, most studies report that >75% of patients had no evidence of steatosis after weight loss surgery. Fourteen studies have evaluated the effects of bariatric surgery on NASH; all of them showed improvements in ballooning and lobular inflammation. In patients with NAFLD, regression of fibrosis is possible when at least 10% of body weight is lost. Among 18 studies which describe postoperative fibrosis score on liver biopsy, 16 (89%) studies showed regression of fibrosis. However, a Cochrane review concluded that the current lack of randomized clinical studies prevents a definitive assessment of the benefits and harms of bariatric surgery as a therapeutic approach for patients with NASH.

Until the last two decades, bariatric surgery conferred high risks of complications, including steatohepatitis and liver failure from jejunoileal bypass surgery. However, recent reviews and meta-analyses of 161,756 patients receiving bariatric surgery in US describe an overall mortality of 0.22% and 30 day morbidity of 9.8%. Furthermore, the mortality and morbidity rate of laparoscopic Roux-Y gastric bypass is similar to laparoscopic cholecystectomy. Weingarten et al reported on 340 patients who underwent laparoscopic bariatric operations and had intraoperative liver biopsies. The complication rate did not differ significantly across NASH categories. However, surgery for individuals with
established cirrhosis caused by NAFLD is associated with higher perioperative risk. A recent review reported an overall operative morbidity in cirrhosis of 21%, with 6.6% risk of liver decompensation and 2.5% late surgery-related mortality rate patients where the majority of these patients are Child-Pugh class A. The operative mortality rate is also significantly higher in decompensated cirrhosis than those with compensated state (16.3 % and 0.9 % respectively). 

Non-alcoholic fatty liver disease (NAFLD) is present in 65% to 90% of bariatric surgery patients, and up to three quarters of these patients suffer from NASH. The role of screening is not established for patients with NAFLD and NASH. Most patients with morbid obesity have NAFLD, and the surgical plan will seldom be altered depending on the presence of NASH or simple steatosis. However, if patients are known to have cirrhosis at the time of referral for consideration of bariatric surgery, the cause of cirrhosis should be elucidated, and patients evaluated for hepatic function and presence of portal hypertension. Specifically, they should undergo an upper endoscopy, looking for varices and/or portal gastropathy. Computed tomography (CT) can be useful in detecting intraabdominal varices (and patent umbilical vein) not seen endoscopically and can reveal the presence of clinically indeterminable ascites and splenomegaly. Overall, the literature suggests that in patients with well compensated state (Child-Pugh class A) without evidence of portal hypertension, bariatric surgery will result in slightly higher but acceptable morbidity and mortality. This will delay progression of liver disease to decompensation and also increase the candidacy for liver transplantation.
7.6 Liver transplantation

In the United States, nonalcoholic steatohepatitis (NASH) is now the second most common indication for liver transplantation and is the most rapidly growing indication for liver transplantation in patients with hepatocellular carcinoma (HCC).\textsuperscript{115-117} The indications for liver transplantation in NASH cirrhosis and HCC are the same as those for other etiologies of liver disease.\textsuperscript{118} Overall survival rates after liver transplantation in patients with NASH is also the same as those for other indications, but patients with NASH are more likely to die post-transplant because of cardiovascular disease (CVD) and chronic kidney disease (CKD).\textsuperscript{119, 120} This is related to the fact that patients with NASH are usually older and are complicated by metabolic risk factors such as obesity and diabetes mellitus predisposing them to increased CVD and CKD.\textsuperscript{115} Because of the risk of prolonged ventilation, poor wound healing, higher rate of primary graft non-function and increased infectious complications, patients with severe obesity (BMI > 40Kg/m\textsuperscript{2}) and NASH cirrhosis may even be considered unfit for liver transplantation unless efforts are made pre-operatively to reduce body weight with individualized plans of lifestyle modifications.\textsuperscript{121, 122} In exceptional circumstances, simultaneous bariatric and liver transplantation surgery has also been performed in patients with NASH cirrhosis and obesity.\textsuperscript{123} Similar to obesity, patients with NASH and diabetes mellitus with poor glycemic control are at increased post-operative risk for infections, CVD and acute cellular rejection. Hence, a thorough evaluation for diabetes and good glycemic control are essential for good post-operative outcome in such patients.\textsuperscript{124} Since patients with NASH cirrhosis are at increased risk for CVD which could be responsible for higher operative and post-operative mortality, a detailed cardiovascular assessment is a must for patients with NASH cirrhosis prior to liver transplantation.\textsuperscript{125} Even though recurrent NASH and severe fibrosis occurs infrequently, the risk of recurrence of NAFLD in patients with
NASH cirrhosis undergoing liver transplantation may approach 100% at five years.\textsuperscript{126} NAFLD can even develop de-novo in patients undergoing liver transplantation for other etiologies because of the post-transplant metabolic syndrome (PTMS) related to immunosuppression and multiple other factors.\textsuperscript{127} The treatment of post liver transplantation NAFLD/NASH is largely with lifestyle modifications with no data on the use of Pioglitazone or Vitamin E. Management of PTMS would require limited use of CNIs and steroids and bariatric surgery in exceptional patients with severe obesity.\textsuperscript{128,129}

### 7.7 Management of NASH-related HCC

#### 7.7.1 Treatment choice and outcomes; any difference from HCC of other etiologies?

NAFLD increases the risk of HCC and intrahepatic cholangiocarcinoma.\textsuperscript{130-132} Obesity and diabetes, which are the main causes of NAFLD, have also been revealed as risk factors for liver cancer by clinical and experimental studies. A synergistic effect of NAFLD, obesity, and diabetes may play a role in the development of liver cancer. As with other liver diseases, advanced fibrosis and cirrhosis are the most important risk factors for HCC.\textsuperscript{133-135} In addition, advanced age and male sex also increase the risk of HCC.

Compared to HCC of other etiology, HCC in patients with NAFLD is complicated by diabetes, hypertension, and cardiovascular diseases. NAFLD-HCC was mostly detected by outside surveillance. It was larger and showed more of an infiltrative pattern at the time of diagnosis. Cirrhosis was present in only about 50% of patients with NAFLD-HCC.\textsuperscript{136-143} These patients had a similar recurrence rate and survival rate compared to those with other etiology (3-year survival rate: 70-80%).\textsuperscript{137,139-141} However, HCC in NASH is difficult to evaluate because histological diagnosis is required for the diagnosis of NASH, which can lead to selection bias. Furthermore, in end-stage, the characteristic features of NASH disappear.
(i.e., burned-out NASH), and a diagnosis of NASH can no longer be made. There are no special treatments for liver cancer based on NASH/NAFLD. It should be treated according to the HCC guidelines.¹⁴⁴-¹⁴⁷

Recommendation Statements

7.1 Lifestyle intervention programs can achieve reduction in liver fat content, resolution of steatohepatitis in all patients, as well as reduction in liver fibrosis. (A1)

7.2 A multidisciplinary approach to management is important to ensure motivation and continued participation in intervention programs. (B2)

7.3 Vitamin E may improve serum aminotransferases and liver histology in non-cirrhotic non-diabetic NASH adults but further studies are needed before firm recommendations can be made. (A2)

7.4 Pioglitazone cannot be recommended for general use in patients with NASH but could be considered for short-term use in patients with pre-diabetes or type 2 diabetes. Careful assessment should be made of co-morbid conditions (osteoporosis, cardiac function) that may influence suitability of this agent in these patients. (B2)

7.5 The safety of pioglitazone in patients with cirrhosis has not been adequately established. Therefore, pioglitazone should be used with caution in cirrhotic patients (C2)

7.6 Pentoxifylline is not recommended as a treatment for NAFLD/NASH. (B2)

7.7 Metformin does not have direct effect on the histology of NASH. However, its other benefits are well documented. Metformin should remain the first-line anti-diabetic agent in patients with T2DM. (A1)

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7.8 Liraglutide reduces cardiovascular complications and possibly improves NASH. It may be considered in diabetic patients with NAFLD/NASH. However, its use in non-diabetic patients cannot be recommended until more definitive data becomes available. (B2)

7.9 There is insufficient data to support the use of DPP-4 inhibitors as a treatment for NASH. (C2)

7.10 Obeticholic acid may improve NASH and fibrosis, but results observed in the Japanese population are inconsistent. As well, it also causes pruritus and atherogenic lipid profile. Until further information from the phase 3 study is available, off-label use of obeticholic acid in NASH patients cannot be recommended. (B2)

7.11 n-3 polyunsaturated fatty acids may reduce liver fat and improve blood lipid profile, but do not appear to have beneficial effects on liver histology. (B2)

7.12 When indicated, statins may be administered to patients with NAFLD who have mild elevation of transaminases or compensated cirrhosis. (A1)

7.13 Bariatric surgery can improve the histology of NASH and reduce long-term mortality, but its use should be limited to patients with class II obesity (BMI >32.5 kg/m\(^2\) in Asians and 35 kg/m\(^2\) in Caucasians). Its effect on improving liver-related complications is as yet unproven but it may reduce overall mortality through its effect on cardiovascular factors. (B1)

7.14 Lifestyle management should be offered before and after liver transplantation in patients with NASH-related end-stage liver disease. (B2)
8. Special groups

8.1 Children and adolescents

The management of NAFLD in children consists of treating liver disease itself as well as co-morbidities such as obesity, hyperlipidemia, insulin resistance, T2DM, and cardiovascular disease. No pharmacologic treatment has yet been shown to be effective for NASH in children.

8.1.1 Diet and lifestyle modification

Lifestyle modification is the mainstay treatment for NAFLD in children. In the meantime, it also improves the comorbidities. However, it is very difficult to achieve sustained lifestyle change, especially in children.

In adults, moderate weight loss of 7-10% was associated with reduced liver fat, NASH resolution, and even reduction of fibrosis. However, in children, no sufficient data to define the optimal lifestyle intervention. Nobili et al. tested the effectiveness of 1-year lifestyle modification in 84 obese Italy children with biopsy-proven NAFLD. Overall, patients losing 5% or more of body weight had improvements in ALT levels. Another pediatric study from Italy showed 2 kg weight loss could achieve a decrease in ALT from 54 to 37 U/L and hepatic fat fraction from 15.2% to 6.4% within one year.

8.1.2 Vitamin E

Oxidative stress is a key mechanism of hepatocellular injury, so vitamin E would be expected to have some effect in NAFLD. The TONIC trial reported a modest benefit of
vitamin E in NAFLD in children by showing some improvement in ballooning degeneration only.\textsuperscript{151}

### 8.1.3 Probiotics

Gut dysbiosis has been known to play a key role in the pathogenesis of NAFLD and probiotics seem to be a logic target to benefit NAFLD. In obese children, administration of VSL\#3, a mixture of eight probiotic strains, for 4 months decreased steatosis and body mass index, but not serum ALT.\textsuperscript{152} Another randomized trial with 8 weeks of Lactobacillius GG reported a significant improvement in serum ALT, but not in liver ultrasound assessment.\textsuperscript{153}

### 8.1.4 Omega-3 fatty acids

Data regarding the effect of omega-3 fatty acids on NAFLD are inconsistent.\textsuperscript{154} A randomized controlled trial reported docosahexaenoic acid supplementation might decrease liver fat and increased insulin sensitivity in children.\textsuperscript{155} Another small trial by Janczyk et al. found no effect of n-3 fish oil in either liver steatosis or serum ALT.\textsuperscript{156}

### 8.1.5 Cysteamine Bitartrate Delayed Release

Glutathione is a major hepatocellular antioxidant. Cysteamine is a small molecule which can be taken up into cells and facilitate glutathione synthesis. A recent randomized controlled trial of 169 children with NAFLD reported that cysteamine bitartrate delayed release improved serum ALT, but not liver histology over 52 weeks.\textsuperscript{157}
8.2 Fatty liver in patients with viral hepatitis

8.2.1 Prevalence and significance of hepatitis C virus (HCV)-associated non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH)

Nonalcoholic fatty liver disease (NAFLD) or steatosis occurs commonly (around 50%) in patients with hepatitis C virus (HCV) infection, whereas non-alcoholic steatohepatitis (NASH) can be documented in 4%-10% of HCV-infected subjects.\textsuperscript{158-160} For the majority of patients infected with HCV genotype non-3, steatosis is usually associated with the presence of metabolic derangement and insulin resistance, and is called “metabolic steatosis”. HCV genotype 3 infection itself may directly influence fat deposition in the liver, which is called “viral steatosis”; accordingly, HCV genotype 3 infection is associated with the highest prevalence of steatosis.\textsuperscript{161-163} Genetic background of the hosts has been found to predispose patients to the development of steatosis.\textsuperscript{164} Irrespective of insulin resistance, HCV-associated NAFLD contributes to the progression of underlying liver fibrosis and the development of hepatocellular carcinoma by the acceleration of liver necroinflammation and oxidative stress.\textsuperscript{165-167} Extrahepatically, NAFLD is associated with the presence of metabolic syndrome, type 2 diabetes, and atherosclerosis.\textsuperscript{168} From the therapeutic point of view, HCV-related metabolic steatosis may impair the response to interferon-based therapy\textsuperscript{169-172}, whereas genotype 3-associated viral steatosis was found to decrease the response to new oral direct antiviral agents (DAAs).\textsuperscript{173} In summary, NAFLD occurs commonly in patients with HCV infection, which in certain genotype is induced by the virus itself. NAFLD significantly impacts progression of the liver disease, therapeutic response, and the development of some extrahepatic cardiovascular diseases.

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8.2.2 Prevalence and significance of hepatitis B virus (HBV)-associated NAFLD and NASH

Hepatitis B virus (HBV) infection is a major etiology of chronic liver disease worldwide, and NAFLD has emerged as a common liver disorder in the general population. Therefore, the number of patients with co-existing chronic hepatitis B (CHB) and NAFLD grows rapidly. Interestingly, patients with CHB were found to have a lower evidence of NAFLD in comparison with the general populations and subjects with chronic HCV infection. Specifically, around 14% – 56% of patients with chronic HBV infection had evidence of fatty liver. The mechanism is possibly due to a lower frequency of dyslipidemia profile in patients with chronic HBV infection. Recent studies aimed to explore the relationship between CHB and NAFLD from different aspects.

Although numerous cross-links have been found between HBV infection and NAFLD pathogenesis, the association of HBV with metabolic syndrome, insulin resistance, and the risk of arteriosclerosis is still inconclusive. Notably, obesity, diabetes, and metabolic syndrome may accelerate the progression of liver disease in patients with chronic HBV infection and synergistically induce cirrhosis or even hepatocellular carcinoma development. Recent prospective cohort studies further demonstrated that metabolic syndrome may increase the risk of cardiovascular events but not hepatic events and death. Finally, from the therapeutic point of view, a recent review demonstrated that co-existing NAFLD did not influence the response to oral nucleos(t)ide analogue or interferon therapy.
Recommendation Statements

8.1 Until further data from clinical trials become available, no pharmacological treatment can be recommended for children and adolescents with NAFLD/NASH. In this situation, lifestyle modification should be recommended. (B2)

8.2 Hepatic steatosis occurs commonly in patients with hepatitis C virus (“HCV”) infection, and is associated with extrahepatic manifestations. HCV-associated steatosis contributes to the progression of underlying liver fibrosis and the development of hepatocellular carcinoma, and may impair the response to interferon-based therapy. (B2)

8.3 The prevalence of NAFLD in patients with HBV infection appears to be lower than that in the general population. The presence of metabolic syndrome may accelerate the progression of liver disease in patients with chronic HBV infection. (B1)

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Table 1. Existing pharmacological agents and agents entering phase 3 development with potential effect on NASH

<table>
<thead>
<tr>
<th>Drug/drug class</th>
<th>Mode of action</th>
<th>Improve NASH</th>
<th>Improve liver fibrosis</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin E</td>
<td>Anti-oxidant</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Insulin sensitizer</td>
<td>Yes</td>
<td>Inconsistent results</td>
<td></td>
</tr>
<tr>
<td>Elafibranor</td>
<td>Peroxisome proliferator-activated receptor-alpha and delta agonist</td>
<td>Yes</td>
<td>Only in patients with improvement in NASH</td>
<td></td>
</tr>
<tr>
<td>Pentoxifylline</td>
<td>Anti-inflammatory; weak anti-tumor necrosis factor-alpha action</td>
<td>Possible?</td>
<td>One small RCT only</td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td>Insulin sensitizer</td>
<td>No</td>
<td>No</td>
<td>No effect – several meta-analyses</td>
</tr>
<tr>
<td>Glucagon-like peptide-1 receptor agonists</td>
<td>Reduce appetite and increase insulin sensitivity</td>
<td>Yes</td>
<td>May prevent fibrosis progression</td>
<td>Given as injections and may cause gastrointestinal upset</td>
</tr>
<tr>
<td>Dipeptidyl peptidase-4 inhibitors</td>
<td>Increase incretin levels</td>
<td>Unknown</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>Obeticholic acid</td>
<td>Stimulates farnesoid X receptor</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Omega-3 fatty acids</td>
<td>Anti-inflammatory and potential effects on lipid metabolism</td>
<td></td>
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