Position statement on the diagnosis and management of non-alcoholic fatty liver disease

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ABSTRACT

مرض الكبد الدهني غير الكحولي يعتبر مشكلة وعبئاً صحياً محلياً وعالمياً، حيث أنه من أكثر أمراض الكبد شيوعًا في العالم ومن أكثر مسببات إرتفاع انزيمات الكبد في العديد من الدول المتقدمة. كما يُعد مرض الكبد الدهني غير الكحولي سببا رئيسا لتليف الكبد ويسجل كثاني أكبر سبب لزراعة الكبد في العديد من الدول. ويرتبط مرض الكبد الدهني غير الكحولي عادة مع متلازمة التمثيل الغذائي. يعد التهاب الكبد الدهني غير الكحولي هو النمط الظاهري والمرحلة التقدمية للمرض، ويشخص عادة عن طريق عمل خزعة كبدية بسبب الأداء الأضعف للطرق الأخرى. ويعتبر تغيير نمط الحياة غذائياً مع إنقاص الوزن وعمل الرياضة الوسيلة الاكثر فاعلية لعلاج المرض ومنع تطورة بالرغم من وجود العديد من الأبحاث على كثير من الأدوية في مراحل الدراسة الثانية والثالثة، لكن لا يوجد دواء معتمد حتى الآن. وبالرغم من المعدلات العالمية المثيرة للقلق فأنه لا توجد دراسات مجتمعية محلية حول انتشاره أو إرشادات وتوصيات وطنية للمارسين حول المتابعة والعلاج للمصابين بهذا المرض، لذا يهدف هذا الاستعراض لملء جزء من هذه الفجوة.

Non-alcoholic fatty liver disease (NAFLD) is a major national and international health burden. It is one of the most common liver diseases worldwide and the most common cause of abnormal liver enzymes in many developed countries. Non-alcoholic fatty liver disease is also known as an important cause of cryptogenic cirrhosis and second leading cause for liver transplantation. It is commonly associated with metabolic syndrome. Non-alcoholic steatohepatitis (NASH) is the progressive phenotype of NAFLD. In spite of promising performance of non-invasive tools, liver biopsy remains the gold standard test for NASH diagnosis. Over decades, many drugs have been investigated in phase 2 and 3; however, no approved therapy to date. Despite the alarming global rates of NAFLD, there are no local community-based studies on the prevalence of NAFLD or local practice guidelines on its management; this expert review aims to fill this gap.

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Non-alcoholic fatty liver disease (NAFLD) is one of the most common liver diseases worldwide and is the most common cause of abnormal liver enzymes in many developed countries. Non-alcoholic fatty liver disease is also known as an important cause of cryptogenic cirrhosis. Non-alcoholic steatohepatitis (NASH)-related cirrhosis is currently the second most common indication for liver transplantation in the United States of America (USA).[1] However, with the evolution of hepatitis C virus (HCV) therapy, NASH is anticipated to be the leading cause of liver transplantation in the near future. Non-alcoholic fatty liver disease is commonly associated with metabolic syndrome (MetS), and there is accumulative evidence indicating that NAFLD is an independent risk factor for cardiovascular disease (CVD) in adults.[2]

Non-alcoholic fatty liver disease is defined by the presence of steatosis in >5% of hepatocytes according to histological analysis or by a proton density fat fraction assessed by proton magnetic resonance spectroscopy (1HMRS) or quantitative fat/water selective magnetic resonance imaging (MRI).[3,4] This definition requires the absence of significant alcohol intake, other liver

Summary points:

NAFLD is defined by the presence of ≥5% of fat in the liver with no significant alcohol use or other causes of hepatic steatosis.

NAFLD is a spectrum of liver diseases ranging from hepatic steatosis to NASH and liver cirrhosis, including a significant portion of cryptogenic cirrhosis.

NAFLD is one of the most common liver diseases worldwide.

NASH is the second most common indication for liver transplantation in developed countries.

disorders or the use of steatosis-induced medications/toxins, such as amiodarone or tamoxifen. Non-alcoholic fatty liver disease is a spectrum of diseases ranging from non-alcoholic fatty liver (NAFL), in which fat accumulates in liver cells with no significant inflammation, to NASH, where fat accumulates with varying degrees of necroinflammation, evidence of cellular injury and fibrosis, which can progress to cirrhosis and liver failure.[4]

Despite the alarming global rates of NAFLD, there are no community-based studies on the prevalence of NAFLD in Saudi Arabia (SA) or local guidelines on its management; this expert review aims to fill this gap.

Methods. This position statement and these recommendations have been prepared by a panel of experts chosen by the Saudi Association for the Study of Liver Diseases and Transplantation (SASLT) Board. The recommendations are primarily based on the best available evidence from existing publications, after extensive search in indexed and non-indexed articles in the PubMed, Scopus and Google scholar. In the absence of such evidence, the experts' personal experiences and opinions have been considered. Wherever possible, the level of evidence and recommendations are cited. The recommendations have been graded according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.[5] The strength of recommendations reflects the quality of underlying evidence. The quality of the evidence in the recommendations has been classified into one of 3 levels: A) high, B) moderate, or C) low and very low. The GRADE system offers 2 grades of recommendation: 1) strong or 2) weak. The Appraisal of Guidelines for Research and Evaluation (AGREE) Instrument was adapted as possible for this short statement.

Disclosure. Authors have no conflict of interests, and the work was not supported or funded by any drug company. This position statement from the Saudi Association for the Study of Liver Diseases and Transplantation (SASLT) is issued to support the local medical community (primary care, family physicians, internists, gastroenterologists and other healthcare providers who handle fatty liver disease or its related metabolic risk factors) with concise, up-to-date information and practical guides on the management of fatty liver disease. There is a growing concern regarding the increasing rates of obesity and metabolic syndrome in the Saudi community as well as associated fatty liver disease, which has become the second leading cause of liver transplantation in the country with a lack of effective approved therapy and robust local data on the natural history of the disease.

Prevalence. The lack of definitive simple tests for diagnosing NAFLD as well as the variety of diagnostic tools and criteria used in various studies pose a challenge in studying the epidemiology of NAFLD and explaining the differences in reported prevalence. Accumulating evidence has shown that the prevalence of NAFLD is increasing in many parts of the world. Compared to a decade ago, currently, the prevalence of NAFLD in the USA has doubled, which parallels the increased prevalence of obesity and insulin resistance (IR).[6]

In a recent large systematic review, the global prevalence of NAFLD was estimated to be 25%, with the highest prevalence in the Middle East (32%) and South America (31%) and the lowest in Africa (14%).[7] In SA, the prevalence of NAFLD ranges from 7-30%. A recent modeling study estimated the prevalence of NAFLD in SA to be 25.7% of individuals (8,451,000 people) and modeled the future burden in 2030 to be 48% (12,534,000 people).[8]

The prevalence of diabetes mellitus (DM) in SA has been reported to be one of the highest in the world. In a recent, large, population-based study, DM prevalence was 40% for subjects aged >45.[9] In another recent study, 72.8% of DM patients in SA have fatty liver according to ultrasound criteria.[10]

Non-alcoholic fatty liver disease and NASH prevalences confirmed by biopsy have been reported in SA to be 76% and 40%, respectively, in obese children and adolescents who underwent sleeve gastrectomy,[11] and the estimated overall prevalence of obesity in the country is 30% in males and 44% in females.[12]

Other components of MetS associated with NAFLD include hypertension and hyperlipidemia; the prevalence of these 2 conditions in SA is estimated to be

Summary points:

NAFLD global prevalence is estimated to be 25%, with the highest prevalence in the Middle East, with 32% affected.

NAFLD estimated prevalence in SA ranges between 25% and 48% and is as high as 73% among Saudi individuals with diabetes.

approximately 26% and 54%, respectively.[13] It is also noteworthy that in SA and in some other countries, there has been a shift in the trend of indications for liver transplantation from viral hepatitis to NASH-related cirrhosis.[14]

Pathogenesis. The hallmark of NAFLD is triglyceride accumulation in the cytoplasm of hepatocytes, which results from an imbalance between lipid acquisition (namely, fatty acid uptake and de novo lipogenesis) and removal (namely, mitochondrial fatty acid oxidation and export as a component of very low-density lipoprotein particles).

Accumulating evidence from cellular and molecular studies of patient and animal models has led to a "multiple hit" hypothesis, which considers multiple insults acting together on genetically predisposed subjects to induce NAFLD and its progression. Such hits include nutritional factors, IR, several fat-derived hormones, defects in mitochondrial structure and function, gut microbiota and genetic and epigenetic factors.[15]

Genome-wide association studies and large candidate gene studies have identified some robust genetic modifiers. In addition to the genetic factors that predispose patients to IR or MetS, the I148M PNPLA3 variant has been identified as the major common genetic determinant of NAFLD progression and of the risk of hepatocellular carcinoma (HCC).[16] Other variants with moderate effects such as TM6SF2, MBOAT7 and GCKR have also been shown to have significant contributions.[17]

Natural history. Several community and hospital-based studies have contributed to our understanding of the natural history of NAFLD; however, most follow-up studies on histological changes in NAFLD have had small sample sizes and insufficient follow-up.

Non-alcoholic fatty liver disease has often shown favorable outcomes; in contrast, NASH has been recognized to progress to end-stage liver diseases and HCC. Progression to cirrhosis is less predictable in NASH than in other chronic liver diseases. Several factors are reported to be associated with disease progression, such as older age, MetS, IR, serum ALT, and the presence of inflammation on initial biopsy.[18] The mortality rate associated with NAFLD is thought to be attributable to CVD. The relationship with MetS likely is a bidirectional with several recent studies have verified that NAFLD itself is an independent risk factor for various other metabolic diseases.[19]

Non-alcoholic fatty liver disease patients are at risk of developing HCC, especially in patients with NASH and cirrhosis; however, HCC can develop in absence of cirrhosis. In a large systematic review, patients with NASH and cirrhosis had a consistently higher risk of developing HCC, with a cumulative incidence of 2.4% to 12.9% over a follow-up period of 3 to 7 years,

Summary Points:

NAFLD is highly associated with MetS and its different components.

NAFLD patients have a higher mortality than the general population, mostly due to CVD and liver-related morbidity and mortality.

NAFLD can lead to HCC with or without cirrhosis

while patients with NAFLD or NASH with no cirrhosis had a minimal risk ranging from 0% to 3% over a period of 20 years.[20] When compared to HCV-related HCC, NAFLD-related HCC occurred at a lower incidence and usually with larger tumors at presentation, which were less likely to be amenable to curative therapy; however, the overall survival is comparable.[20]

Diagnosis. The diagnosis of NAFLD requires confirmation of extra fat in the liver by noninvasive or invasive methods in addition to the exclusion of other liver disease etiologies such as significant alcohol use and medications.

Liver biopsy. Liver biopsy (LB), with its limitations and potential complications, is still the gold standard for NASH diagnosis and for assessing fibrosis progression; however, it is not recommended in all patients with NAFLD. Most international guidelines recommend LB for patients with risk factors for advanced fibrosis with NASH, when there is diagnostic uncertainty, or to rule out other causes of liver disorders. Some guidelines suggest LB for patients with NAFLD who are undergoing other unrelated surgical procedures.[3,4]

The presence of >5% steatosis in hepatocytes is now the accepted minimum criterion for the histological diagnosis of NAFLD, while the minimum histologic criteria for NASH are the presence of steatosis, hepatocellular ballooning, and necroinflammation,

typically in zone 3. The presence of fibrosis is not required for a diagnosis of NASH, although it is an indicator of disease progression and is the strongest histologic predictor of prognosis.

Noninvasive methods. Several noninvasive diagnostic tools have been proposed and assessed in NAFLD. These tools generally fall into 2 categories: imaging-based or blood tests. The targets of their use and capabilities are to define one or more of the following: the a) identification and quantification of hepatic steatosis, b) prediction of NASH, and/or c) prediction of advanced fibrosis or cirrhosis. These methods, although in use, have inherent limitations in the diagnosis and assessment of NAFLD. The most important methods are summarized in **Table 1**.

Serum biomarkers. Several clinical and biochemical markers have been investigated to predict the presence of NASH and differentiate it from simple steatosis (NAFL). These include clinical (age, gender, DM, BMI), biochemical (aminotransferases, bilirubin and ferritin), and metabolic (glycated hemoglobin, insulin and HOMA-IR and lipid) markers. Some of these biomarkers have been independently validated.

The NAFLD fibrosis score (NFS) is one of the most thoroughly validated scores for the diagnosis of fibrosis in NAFLD patients. It is a simple predictive model (which includes age, impaired fasting glucose/DM, BMI, platelets, albumin and AST/ALT ratio). This score has been validated in multiple studies with an estimated area under the receiver operating curve (AUROC) of 0.85 (95% CI 0.81-0.90).[21] The NFS has the advantage of simplicity and the ability to provide prognostic information about liver complications and mortality.[21] In addition, the NFS has been endorsed by several guidelines and can be calculated online (http://nafldscore.com/). Its application for use is limited by the finding that a significant percentage (20-58%) of patients fall between the 2 proposed cutoff values and will have an indeterminate score. Therefore, the NFS serves best for excluding advanced fibrosis/cirrhosis and could be used as a first line test to identify individuals at low risk for advanced disease.

The FIB-4 score has been validated for the evaluation of fibrosis in patients with NAFLD. In one of the studies using LB as the control comparative arm; the FIB-4 score had the best diagnostic accuracy for advanced fibrosis (AUROC 0.86), and it was better than the aspartate aminotransferase (AST)/alanine aminotransferase (ALT), ratio (AUROC 0.83), NFS score (AUROC 0.81), BARD (AUROC 0.77) and AST to platelet ratio index (AUROC 0.67).[22] In a recent systemic review and meta-analysis that assessed several of these noninvasive tests, the NFS and FIB-4 seemed to offer the best diagnostic performance for detecting advanced fibrosis in patient with NAFLD.[23]

Table 1- Noninvasive methods for Non-alcoholic fatty liver disease diagnosis and assessment.*

Aim	Serum markers	Radiology based
Diagnosis/quantification of steatosis	Steato test Fatty liver index	Liver ultrasound CAP MRI
Diagnosis of NASH	Liver enzymes NASH test	---
Diagnosis/staging of fibrosis	AST/ALT Ratio APRI NFS FIB-4 FibroTest	Transient elastography. Acoustic radiation force impulse elastography. Magnetic resonance elastography Supersonic shear imaging

*Only methods commonly available in routine practice and supported by high-quality evidence are given here. CAP - controlled attenuation parameter, MRI- magnetic resonance imaging, APRI- aspartate aminotransferase to platelets ratio index, NFS - NAFLD fibrosis score, FIB-4 - Fibrosis-4 score, NASH -Non-alcoholic steatohepatitis

Radiology-based tools. One of the most popular imaging-based tools for estimating fibrosis is transient elastography (TE). Most of its validation studies are on viral hepatitis; however, recently, several studies have assessed the use of TE for fibrosis in NAFLD patients, alone or in combination with other tests. The combination of noninvasive tests and TE improves diagnostic accuracy in NAFLD; pooled sensitivities and specificities of TE to diagnose F ≥2, F ≥3 and F4 disease in NAFLD patients were 79% and 75%, 85% and 85%, and 92% and 92%, respectively,[24] Liver stiffness measurements (LSMs) often fail in obese patients, but the success rate might be improved with the use of the XL probe. In a recent USA cohort with NAFLD compared with LB, the median LSMs for patients with and without F3-F4 (advanced) fibrosis were 14.4 kPA (12.1-24.3) and 6.6 kPA (5.3-8.9), respectively. The optimal LSM cutoff for advanced fibrosis was 9.9 kPA (sensitivity 95% and specificity 77%). In addition, 100% of patients with LSM <7.9 kPA did not have advanced fibrosis. The AUROC was 0.93 (95% CI: 0.86-0.96) for the detection of F3-F4 fibrosis. This was superior to the AUROC for NFS 0.77, p=0.0125. A comparison of supersonic shear imaging (SSI), fibroscan, and acoustic radiation force impulse (ARFI) with LB for the diagnosis of different stages of liver fibrosis in NAFLD showed better performance of SSI and fibroscan over ARFI, with even slightly better but similar performance of SSI over fibroscan.[26]

Summary Points:

NAFLD is usually diagnosed with imaging showing the presence of increased liver fat.

The most common presentations of NAFLD are incidental findings of elevated liver enzymes and imaging showing fatty liver disease.

NASH patients may have transaminases within the normal range.

Noninvasive diagnostic tools can be used to assess and stage NAFLD.

Liver biopsy is still the gold standard for NASH diagnosis and to assess fibrosis.

The controlled attenuation parameter (CAP) provides an assessment of steatosis simultaneously with LSMs. The CAP has been assessed in several studies for the diagnosis and grading of steatosis, with overall good performance. In a recent meta-analysis of 11 studies, the AUROC for the diagnosis of steatosis grades were 0.86, 0.88 and 0.94 for the diagnosis of steatosis stage ≥S1, ≥S2, ≥S3, respectively.[27] Several cutoff values for each grade of steatosis have been proposed in different studies.

Magnetic resonance elastography is an excellent tool for the assessment of liver steatosis, and it may perform better than TE. However, TE has the advantage over MRI in terms of easy availability, cost and time taken for the tests. Therefore, TE is an economically attractive alternative to LB and other noninvasive tests, especially for patients with advanced liver fibrosis.[28]

Initial assessment of suspected NAFLD case. The most common presentation scenario of NAFLD is incidentally discovered high liver enzymes (typically

Table 2 - Suggested work-up and monitoring of patient with non-alcoholic fatty liver disease.

Assessment		Timing
	Signs and symptoms of liver-related disease and associated comorbidities	Initial visit Every 3-6 months
Clinical	Alcohol consumption Other causes of steatosis (such as medications)	Initial visit
	Weight Body mass index	Initial visit Every 3-6 months
Routine tests	Complete blood count International normalization ratio liver function test	Initial visit Every 3-6 months
Metabolic tests	Lipid Profile Blood glucose HbA1c	Initial visit Every 3-6 months
Tests to rule out other liver disease*	HBV markers and HCV antibodies. Autoantibodies Serum copper and ceruloplasmin Ferritin, iron studies Celiac disease serology	Initial visit
Imaging	Liver ultrasound	Initial visit Every 6 months (in cirrhosis)
Noninvasive test	Fibroscan, controlled attenuation parameter NFS FIB-4 APRI	Initial visit As guided by risk for follow up (according to accessibility)
Liver biopsy	Possible alternative diagnosis High risk for advanced disease	
Upper GI endoscopy	Cirrhosis**	
Additional tests	Cardiac, renal, metabolic, and so forth (As guided by associated comorbidities)	Coordinated with treating physician or other specialties if needed
Multidisciplinary team	Health educator Dietician Other specialties according to comorbidities - diabetologist, cardiologist, bariatric surgery, and so forth	Initial visit or as guided by the case

Frequency of monitoring is guided by risk stratification and response to management lines. *More investigations are needed if diagnosis is not certain. **As guided by the relevant guidelines, NFS - NAFLD fibrosis score, NAFLD - non-alcoholic fatty liver disease FIB-4- Fibrosis-4 score, APRI- aspartate aminotransferase to platelets ratio index.

ALT, AST and sometimes ALP) in asymptomatic patients or the detection of steatosis on imaging done for other purposes, typically in patients with risk factors such as MetS. Occasionally, the initial presentation shows features of advanced liver disease or HCC. The most important steps in evaluating patients with suspected NAFLD are confirming the diagnosis, staging liver fibrosis, assessing liver-related risk, and formulating a management plan.

After the initial clinical assessment, blood tests and imaging are usually needed to confirm diagnosis and rule out other competing liver disorders. **Table 2** summarizes a proposed approach for the initial assessment and monitoring of NAFLD patients.

Screening for NAFLD. Non-alcoholic fatty liver disease is very common, and there is insufficient evidence to justify NAFLD screening in the general population given the high prevalence of the disease, lack of a definitive simple diagnostic test and lack of effective therapy. However, it may be prudent to screen only high-risk groups; this topic is debatable given the challenges in addition to a lack of strong supporting evidence and the cost-effectiveness of this approach. There is no consensus on screening methods among the guidelines of the major international societies (**Table 3**).[3,4,29] Thus, screening of high-risk patients, such as type 2 DM, MetS, or obese patients, is suggested using simple available tools such as liver enzyme tests and abdominal US. Some experts do not support systematic routine screening in high-risk individuals but encourage health care providers taking care of high-risk patients such as diabetic patients to be vigilant for any signs and symptoms of chronic liver disease and to refer the patients for further assessment and management when needed.[30]

Management. The management of patients with NAFLD should target not only liver disease but also associated metabolic disorders. The goals of treating liver disease are to prevent NASH from progressing to advanced fibrosis, to prevent cirrhosis and to prevent the development of complications such as liver decompensation and HCC.

Lifestyle interventions. A large body of evidence suggests a strong relationship between an unhealthy lifestyle and risk factors for NAFLD. Lifestyle modifications including weight loss, exercise and dietary changes should be recommended as the primary interventions for all NAFLD patients. Weight loss is the only intervention with established evidence suggesting benefits and safety, with a clear dose-response association regardless of the type of exercise. Furthermore, this intervention helps in managing and minimizing the risk of associated comorbidities, such as MetS and CVD.

Weight loss and increased physical activity are associated with sustained improvement in liver enzymes, histology, serum insulin levels, and quality of life in patients with NAFLD.[31] The highest rates of NASH reduction, NASH resolution, and fibrosis regression occurred in patients with weight loss ≥10%.[32] The benefit of exercise on liver fat occurred even with minimal or no weight loss.[31,33]

Dietary recommendations for NAFLD patients should include the restriction of daily caloric intake, (approximately 500-1000 kcal/day less than the daily requirement), avoidance of high-glycemic index foods (such as processed foods and beverages high in added fructose), and adoption of a low-fat diet (especially reducing the consumption of saturated fatty acids).[4,34]

Pharmacologic therapy. To date, there are no approved medications for NASH. Several targets have been studied for the pharmacologic therapy of NASH, which include anti-inflammatory, anti-apoptotic, and anti-fibrotic factors as well as metabolic regulators and anti-oxidant pathways.

Insulin sensitizers. Thiazolidinediones (TZD) such as pioglitazone may improve biochemical and

Table 3 - Comparison of guidelines on NAFLD screening.

	EASL (2016)	APASL (2017)	AASLD (2018)	SASLT (2019)
In general population	No	No	No	No
In high-risk group	Yes Obesity, MetS	Yes Type 2 DM, obesity	No	Yes Obesity, Type 2 DM, MetS
Screening tool	Ultrasound and or Liver enzymes	Ultrasound or TE (CAP)	---	Ultrasound or liver enzymes

EASL - The European Association for the Study of the Liver, APASL - Asian Pacific Association for the Study of the Liver, AASLD - American Association for the Study of Liver Diseases, SASLT - Saudi Association for the Study of Liver Diseases and Transplantation, DM - Diabetes mellitus, MetS - metabolic syndrome, TE - transient elastography, CAP- controlled attenuation parameter

histological parameters in NASH patients. The PIVENS trial compared pioglitazone, vitamin E and placebo for 2 years in patients without DM. Pioglitazone in this study improved all histological features (except fibrosis) and achieved resolution of NASH more often than placebo.[35] Subsequent studies and meta-analyses showed histological benefits in diabetic and nondiabetic NASH patients; however, the data on fibrosis improvement are not consistent.[36] Weight gain, bone fractures in women and, rarely, congestive heart failure are concerning potential long-term side effects. Therefore, TZD can be used in DM and non-DM patients with biopsy-proven NASH.

Vitamin E. Vitamin E has been investigated in the treatment of NASH because of its anti-oxidant effect. In the PIVENS study, vitamin E at a dose of 800 IU/D was superior to placebo for the NASH treatment of nondiabetic adult patients; it led to an improvement in liver enzymes in addition to an improvement in steatosis and lobular inflammation but showed no improvement in fibrosis.[35] Similar results have been confirmed in several studies. Concerns exist over the long-term use of vitamin E, especially at doses >400 IU/d, regarding increases in all-cause mortality, prostate cancer, and hemorrhagic stroke. Based on current evidence and potential long-term risks, vitamin E can be used in nondiabetic patients with biopsy-proven NASH.

New emerging therapies for NAFLD. Over the last few years, many new drugs targeting different pathways have been investigated for NASH treatment, although few have gone beyond phase 2. We will discuss briefly some results of phase 2 studies for some medications that have shown potential in phase 3 and for which studies are ongoing.

Obeticholic acid (OCA) is a synthetic Farnesoid-X receptor agonist. In a phase 2 FLINT study, noncirrhotic NASH patients who received OCA had improvements in all components of the NAFLD activity score (steatosis, hepatocellular ballooning, and lobular inflammation) and small improvements in fibrosis compared to those who received placebo. However, pruritus occurred in 23% of patients.[37]

Elafibranor is a dual peroxisome proliferator-activated receptor (PPAR)-α/δ agonist. It improves insulin sensitivity, glucose homeostasis, and lipid metabolism and reduces inflammation. A phase 2 trial in NASH patients without cirrhosis showed the resolution of NASH without a worsening of fibrosis and good tolerance.[38]

Cenicriviroc (CVC) is a dual antagonist of CCR2/CCR5 receptors, which have been shown to play key roles in hepatic inflammation and fibrosis. A phase 2 study showed that 1-year treatment with CVC resulted in a significantly higher improvement in fibrosis without worsening of NASH compared with placebo treatment.[39]

Selonsertib is a selective inhibitor of ASK1, and it leads to an improvement in inflammation and fibrosis. In a multicenter phase 2 trial, selonsertib-treated patients had higher rates of fibrosis improvement and lower rates of fibrosis progression than patients treated with simtuzumab alone over a 24-week treatment period.[40]

Liraglutide is a glucagon-like peptide-1 analogue that can reduce weight, hepatic steatosis, liver enzymes, and IR in NAFLD. In a phase 2 LEAN trial, liraglutide led to significantly more histological resolution of NASH compared to placebo.[41] However, larger studies with long-term follow up are needed.

Drugs commonly used to treat NASH with no proven efficacy. In clinical practice, some drugs are commonly prescribed in patients with NAFLD or NASH, such as metformin, ursodeoxycholic acid, omega-3 fatty acids and probiotics. These drugs may have evidence for biochemical improvement; however, strong consistent evidence for histological improvement is lacking. Thus, these drugs cannot be recommended, although they may be used to treat NAFLD-associated conditions.[3,4]

Bariatric surgery. Obese patients with NASH or MetS may benefit from bariatric surgery; however, NAFLD per se is not an indication for bariatric surgery. Bariatric surgery is associated with a significant improvement in histological and biochemical markers of NAFLD and components of MetS. However, the data are inconsistent and possibly biased, including high heterogeneity of results in reported systematic reviews. Several long-term follow up studies and registration databases have shown a significant reduction in mortality including the risk of CVD, DM and cancer for patients who underwent bariatric surgery.[42,43] In addition, bariatric surgery has been shown to be cost effective for obese-NASH patients, regardless of fibrosis stage.[44]

It is worth mentioning that fibrosis may progress in some NASH patients after bariatric surgery. Therefore, comprehensive liver assessment and postoperative follow-up are mandatory, as ALT is not a reliable marker for liver disease or cirrhosis in bariatric surgery patients with or without NAFLD.[45] Therefore, to avoid deterioration of liver function and to improve outcomes after surgery, proper preoperative assessment of patients including noninvasive tests and possible biopsy during surgery with close medical follow-up post-surgery should be implemented.

Liver transplantation. Non-alcoholic steatohepatitis may go unrecognized until patients present with decompensated liver disease. Non-alcoholic steatohepatitis is currently the second most common indication for liver transplantation in the USA and SA.[1,14] Globally, NASH patients on the waiting list for LT are old and have a high body mass index (BMI), prevalence of type 2 DM, metabolic comorbidities and low glomerular filtration rates. Despite high rates of operative difficulties and postoperative complications, the overall long-term patient and graft survival at 1, 3, and 5 years seems to be similar to those of other indications in most studies, with the main causes of death in patients with NAFLD following LT being sepsis and CV disease.[46]

Statins and NAFLD. Serious liver injury with statins is rare and unpredictable in individual patients, and routine periodic monitoring of liver enzymes does not appear to be effective in detecting or preventing serious liver injury. Hence, the FDA modified labels for statin use, recommending that liver enzyme tests be performed before starting statin therapy and thereafter, as clinically indicated (not routinely).[47]

In statin-treated patients, an increase in liver enzymes may be due to different etiologies. A mild to modest increase in liver enzymes (without evidence of significant liver injury, such as a rise in bilirubin or other clinical evidence) is not necessarily a contraindication to either the initiation or continuation of statins, especially if the clinical presentation and subsequent assessment suggests NASH as the reason for the liver enzyme elevation.[48]

Statins are generally safe to use when indicated in all chronic liver disease, including compensated cirrhosis, autoimmune hepatitis and liver transplant recipients48. A significant body of evidence supports that statins are safe in NAFLD patients, with the main benefit of reducing CVD events, which represent the leading cause of death in this population. Several systematic reviews have shown that statins may improve aminotransferase levels, impede the progression of hepatic fibrosis, reduce portal hypertension, prevent hepatic decompensation in cirrhosis, and reduce all-cause mortality in patients with chronic liver disease.[49] International guidelines support the use of statins when clinically indicated (such as for lowering lipids or for the prevention of CVD) in NAFLD patients, including those with mild elevation of transaminases or compensated cirrhosis, but they are not recommended as a therapeutic option for liver disease, as strong evidence is still lacking.[3,4,50]

Recommendations:

1) In high-risk groups of NAFLD (obesity, MetS), screening for NAFLD by liver enzymes and/or ultrasound is recommended as part of a routine work-up. B2
2) All patients with NAFLD should be assessed for features of MetS. A1
3) NAFLD patients with age >50 and multiple MetS components need to be assessed for advanced fibrosis by noninvasive methods, such as NFS, APRI, FIB-4 or CAP. B1
4) Lifestyle modifications including weight loss, exercise and dietary changes should be recommended as primary interventions for all NAFLD patients. A1
5) Patients with NAFLD and clinical suspicion of advanced fibrosis, high liver enzymes, and advanced fibrosis on noninvasive tests should be referred to a liver disease specialist. C1
6) Pharmacologic therapy should be limited to patients with advanced fibrosis or patients at risk of progression such as patients with high liver enzymes and type 2 DM or MetS. B1
7) Vitamin E can be used in nondiabetic patients with NASH and advanced fibrosis; risks and benefits should be addressed with the patient. B2
8) TZD can be used in diabetic and nondiabetic patients with NASH and advanced fibrosis; risks and benefits should be addressed with the patient. B2
9) Metformin, ursodeoxycholic acid and omega-3 fatty acid are not recommended for the treatment of NASH but can be used if indicated to treat other associated conditions. B1
10) When indicated to reduce cholesterol or prevent CVD, statins can be used in NASH patients. B1
11) Bariatric surgery can be considered in obese patients and NASH. B1
12) Patients with suspected NASH and advanced fibrosis who are undergoing elective surgery should be assessed preoperatively for the presence of cirrhosis and the risk of decompensation. C1
13) NASH patients with liver decompensation or HCC within Milan's Criteria are candidates for liver transplantation evaluation. A1

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