Review Article

Current Management Strategy of Non-Alcoholic Fatty Liver Disease

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease worldwide and is becoming the most common indication for liver transplant in the Western world. The disease spectrum varies from steatosis to non-alcoholic steatohepatitis (NASH), advanced fibrosis, cirrhosis and hepatocellular carcinoma. The global prevalence of NAFLD and NASH varies from 24–25% and 1.5–6.45% respectively among general population. Despite the disease burden and adverse outcome of the condition, no highly effective treatment is currently available for NAFLD. Considering its global prevalence and impact clinicians and researchers from different scientific associations worldwide tried hard to develop high-quality international guidelines to improve the management of NAFLD patients in clinical practice. This paper aims to discuss the management options for NAFLD based on five different well-known international guidelines. These guidelines agree on many points and disagree on some points. Notably these guidelines differ in determining alcohol threshold for defining NAFLD, in screening strategies in high-risk patients, the non-invasive test proposed for the diagnosis of NAFLD and advanced fibrosis in patients with NAFLD, in the follow-up protocols and, finally, in the proposed pharmacological treatment strategy.

Key words*: Non-alcoholic fatty liver disease; Metformin; Non-invasive diagnosis; Pioglitazone; Clinical guidelines*

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Introduction

Excess hepatic fat accumulation (>5% hepatocytes) in the absence of excess alcohol consumption and other conditions that lead to hepatic steatosis is regarded as non-alcoholic fatty liver disease (NAFLD). The disease spectrum ranges from simple fat accumulation (NAFL) to non-alcoholic steaothepatitis (NASH), advanced fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). NAFLD is the leading cause of liver disease worldwide.[1] Owing to increasing rates of obesity, metabolic syndrome (MetS) and diabetes, its incidence and prevalence are rising globally.[2,3] There is uncertainty regarding the true worldwide prevalence and incidence of NAFLD/NASH due to lack of sensitive diagnostic tests besides liver biopsy which remains the gold standard for diagnosis of NAFLD.[4] The Dionysos study[5] reported that the global prevalence of NAFLD is 24–25% among general population. This finding is confirmed by Younossi et al[6] and Younossi et al[7] who reported some regional differences with the highest rates reported in South America (30.45% [95% CI, 22.74–39.44]) and the Middle East (31.79% [95% CI, 13.48–58.23]), followed by Asia, the USA and Europe. The lowest prevalence rate is reported from Africa (13.48% [95% CI, 5.69–28.69]).[7]

In Asia, the pooled regional NAFLD incidence rate was estimated to be 52.34 per 1,000 person-years (95% CI, 28.31–96.77) whereas the incidence rate from the West is estimated to be around 28 per 1,000 person-years (95% CI, 19.34–40.57).[7] There is no direct assessment of the incidence or prevalence of

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NASH as liver biopsy is not feasible in studies of the general population. By indirect means the estimated prevalence of NASH in the general population ranges between 1.5% and 6.45%.[7]

No universal management strategy is currently available for NAFLD. Considering its high prevalence and impact, clinicians and researchers from different scientific associations throughout the world tried hard to develop high-quality international guidelines for improved management of NAFLD patients in clinical practice. These guidelines help clinicians to enrich their knowledge regarding understanding of NAFLD and to adopt appropriate management strategies for patients with NAFLD. This paper aims to discuss the management options for NAFLD based on different well-known clinical guidelines.

Materials and Methods

Five clinical guidelines related to diagnosis and management of NAFLD in the adult population published by renowned scientific associations worldwide were included for analysis of recommendations made by them. The five selected papers were: (1) European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO) (EASL-EASD-EASO)[8] clinical practice guidelines for the management of non-alcoholic fatty liver disease, (2) 'Nonalcoholic fatty liver disease (NAFLD): assessment and management' by the National Institute for Health and Care Excellence (NICE)[9], (3) 'Asia-Pacific Working Party on Non-Alcoholic Fatty Liver Disease guidelines'[10,11], (4) Italian Association for the Study of the Liver (AISF). AISF position paper on nonalcoholic fatty liver disease (NAFLD): updates and future directions[12] and (5) 'The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases (AASLD)'[13].

Definition

According to all the guidelines (EASL, Asia-Pacific, NICE, AISF and AASLD) following two criteria must be fulfilled for defining a case as NAFLD: 1) the clinical evidence of excessive accumulation of fat in the hepatocytes either by imaging techniques or by histology and 2) the absence of other secondary causes of hepatic fat accumulation (significant alcohol consumption, hepatitis C, Wilson's disease, medication use, or hereditary disorders). Among these, the most important is significant ongoing or recent consumption of alcohol.

Guidelines differ regarding the threshold of alcohol in defining NAFLD. According to EASL[8] and NICE[9] guidelines alcohol consumption should not exceed 30 gram/day for men and 20 gram/day for women. In Asia-Pacific guideline[10,11] the limit is two standard drink/day (140 g/week) for men and one standard drink/day (70 g/week) for women. AASLD[13] recommends 21 standard drink/week (294 g/week) for men and 14 standard drink/week for women.

All the guidelines agree to classify NAFLD into simple steatosis (NAFL) and non-alcoholic steatohepatitis (NASH) depending on histological pictures. In NAFL, hepatic fat accumulation is associated with no or minimal lobular inflammation. On the other hand, hepatocyte ballooning and degeneration, diffuse lobular inflammation with or without fibrosis are characteristically found in NASH.[8-13]

EASL[9], Asia-Pacific Guidelines[10,11] and AISF[12] position paper give emphasis on the NAFLD-related HCC, potentially occurring in patients with NAFLD in the absence of cirrhosis[14,15]. Presence of cirrhosis with current or previous histological evidence of steatosis or steatohepatitis (SH) is designated as NASH cirrhosis.[13]

Risk factors associated with NAFLD

According to AASLD guidelines following risk factors are potentially associated with NAFLD.[13]

Common conditions with established associations: Obesity, Type 2 diabetes mellitus, dyslipidaemia (high triglyceride, low high density lipoprotein), metabolic syndrome and polycystic ovary syndrome.

Other conditions associated with NAFLD: Hypothyroidism, obstructive sleep apnoea, hypopituitarism, hypogonadism, pancreato-duodenal resection, psoriasis etc.

A bidirectional association between NAFLD and components of metabolic syndrome (MetS) has been strongly established. Features of MetS are

not only highly prevalent in patients with NAFLD, but components of MetS also increase the risk of developing NAFLD.[7,16]

Outcome in NAFLD

NAFLD is a progressive disorder and a mean annual fibrosis progression rate in baseline NASH is 0.09 (95% CI, 0.06–0.12).[7] Studies demonstrated following outcomes in NAFLD —

1. An overall 10-year survival rate (81.5%) in NASH with advanced fibrosis is not significantly different from matched patients with hepatitis C cirrhosis.[17]
2. NASH is now considered as the second-most common cause of liver transplant (LT) and will be the number one cause of LT in the future, as highly curative antiviral regimen[14,18] are increasingly used for treating more hepatitis C virus (HCV) patients.
3. Importantly, patients with NAFLD are in risk of developing HCC in the long-run. The current HCC incidence rate among NAFLD patients is 0.44 (range, 0.29–0.66) per 1000 person-years.[7] However, the risk for developing HCC in NAFLD patients without cirrhosis is very small.[19]

Screening for NAFLD

Considerable disagreement exists between different guidelines regarding screening of general population for NAFLD because 1) only a small proportion of the general population has severe liver disease because of NAFLD though it is a common cause of CLD[20], 2) type 2 diabetes is associated with higher prevalence of NAFLD, NASH and advanced fibrosis[21-23], 3) effective drug treatment is not still available, 4) lack of sensitive diagnostic tests except liver biopsy which is a risky procedure and 5) cost-effective analysis are scarce[24].

Only EASL, NICE and Asia-Pacific Guidelines[8-10] recommend screening in particular, "high-risk" groups (obesity, MetS and abnormal liver enzymes) either by ultrasonography (NICE and Asia-Pacific guidelines) or by transient elastography (Asia-Pacific guidelines) and liver enzymes (EASL guidelines). On the contrary, AASLD guidelines suggest 'vigilence' in these populations instead of screening as supporting evidence for cost-effectiveness of screening is lacking.[13] Though evidences suggest familial clustering of NAFLD, AASLD guidelines do not recommend systematic screening of family members for NAFLD currently.[13]

Recommended non-invasive test(s) for diagnosis of NAFLD

The objectives of non-invasive assessment is first of all to detect NAFLD among high risk groups, and then to monitor disease progression and treatment response, and to find out the patients with the worst prognosis.[8] The guidelines recommend non-invasive imaging study and liver biochemistry for initial diagnosis and assessment in suspected NAFLD cases.[8-13]

Imaging

Ultrasonography (US)

Abdominal US is an excellent tool for detection of fatty liver in suspected cases or in patients with abnormal liver biochemistry in day to day clinical practice. US is a low cost procedure and widely available. US was found to have excellent sensitivity (92%) and specificity (100%) for the diagnosis of NAFLD. But its sensitivity is low in morbidly obese (BMI >40 kg/m^2) subjects and in case of low hepatic fat content (<20%).[25,26] According to NICE guidelines, all children with metabolic syndrome and type 2 diabetes should undergo screening with liver ultrasound for detection of fatty liver and the test should be repeated in every three years if the first evaluation is negative.[9]

Magnetic resonance imaging (MRI)

MRI is highly sensitive and can detect hepatic steatosis as low as 5–10%. MRI either by proton density fat fraction (H-MRS) or by spectroscopy is considered as the gold standard to assess and quantify hepatic steatosis. But its use is limited by limited availability, high cost and a long time of execution. So it is not recommended in clinical practice.[27] Asia-Pacific guidelines[10,11] and EASL[8] guidelines highlight its role in clinical trials and experimental studies for quantification of hepatic fat and to assess response to treatment.

Transient Elastography (TE)

This is a US-based study. TE by continuous attenuation

parameter (CAP) is used to quantify liver fat content. It has a good sensitivity and liver stiffness is used to measure the severity of NAFLD. Considering its low cost and rapidity of execution Asia-Pacific guidelines recommend CAP as a useful screening tool for NAFLD diagnosis as well as for assessing improvement in hepatic steatosis after lifestyle modification and body weight reduction.[10] On the other hand, EASL guidelines make into notice that there is no head to head comparison of TE with H-MRS for measurement of hepatic steatosis and there are limited data about its ability to discriminate different histological patterns.[8]

Liver biochemistry

Conventional liver biochemistry (ALT, AST and GGT) are not sensitive enough to exclude presence of NAFLD.[8-13] On the other hand abnormal liver biochemistry may mask other causes of liver disease in which steatosis may co-exist. AASLD guidelines also make into notice that elevated serum ferritin and low titers of autoimmune antibodies (especially antinuclear and anti-smooth muscle antibodies) are common features among NAFLD patients. But merely their presence do not necessarily indicate the presence of hemochromatosis or autoimmune liver disease.[13]

A number of biochemical markers, such as TNF-α, IL-6, CRP, pentraxin, ferritin, serum prolidase enzyme activity, soluble receptor for advanced glycation end-product, and cytokeratin-18 have been proposed as useful in predicting the severity of NAFLD/NASH in the past. But none of these markers is sensitive or specific enough for routine clinical use for diagnosis of NAFLD/NASH.[28]

Noninvasive predictor biomarkers and scores of steatosis and steatohepatitis

Currently there is no highly specific and sensitive non-invasive marker for prediction of hepatic inflammation and fibrosis. Therefore clinicians and researchers tried to find out non-invasive biomarkers of disease progression and the development of clinical prediction rules of disease severity.

Fatty Liver Index (FLI)[29] and the NAFLD liver fat score (NFS)[31] are proposed by EASL, Asia-Pacific and Italian guidelines for assessment of liver fat non-invasively. FLI is calculated from serum triglyceride, body mass index, waist circumference, and gamma-glutamyltransferase[29], while NFS is calculated from the presence/absence of metabolic syndrome and type 2 diabetes, fasting serum insulin, and aminotransferases[30]. On the other hand, AASLD guidelines[13] point out that the simultaneous presence of several metabolic diseases is the most potent predictor of hepatic inflammation and adverse outcome in patients with NAFLD. AASLD highlight the lack of evidence of the usefulness of quantifying hepatic steatosis in the routine clinical practice.

Though cytokeratin-18 fragment is a promising biomarker for assessing the presence of inflammation, Asia-Pacific and EASL guidelines agree that the current evidence is not sufficient enough to support its use in clinical practice and that more studies are needed.[8,10] Increased cytokeratin-18 levels have good predicting value for NASH versus normal livers but it cannot differentiate NASH from simple steatosis.[31,32] Though cytokeratin-18 levels decrease in parallel with histological improvement, but its predictive value is not better than ALT in identifying histological response.[33]

In conclusion, according to guidelines, noninvasive tests for detecting NASH and distinguishing it from simple steatosis are not currently available and that liver biopsy is useful for detection of hepatocyte ballooning and lobular inflammation.[8-13]

Noninvasive assessment of advanced fibrosis

Liver-related outcome and survival in NAFLD patients is best assessed by liver fibrosis.[34] As NAFLD is a highly prevalent disorder in general population, detection of fibrosis-cirrhosis by liver biopsy is unfeasible. Cost, procedure-related complications, and intra- and inter-observer variations in reporting the histology are the major drawbacks of liver biopsy, and, therefore, it is usually not recommended in clinical practice, except in circumstances where other causes of liver diseases are to be excluded. Currently, method that can be done easily in daily clinical practice is not available for differentiating grades of liver fibrosis.

Enhanced liver fibrosis (ELF) blood test is cost-effective in predicting liver fibrosis. So, NICE guidelines recommended the ELF blood test to all patients with an incidental diagnosis of NAFLD.[9]

In comparison with other scores, both NFS and Fibrosis 4 calculator (FIB-4) were found to have the best predictive value for advanced fibrosis and these scores are as good as magnetic resonance elastography (MRE) for predicting advanced fibrosis among histologically-proven NAFLD patients.[35] Study showed that NFS has a stronger negative predictive value for advanced fibrosis than the corresponding positive predictive value.[36] EASL, Italian guidelines and AASLD guidelines suggest the use of NAFLD fibrosis score (NFS) and Fibrosis 4 calculator (FIB-4) for identifying patients with risks of advanced fibrosis.[8, 12]

US Food and Drug Administration recently approved transient elastography (TE) to investigate adult and pediatric patients with liver disease. It can detect advanced fibrosis with 95% sensitivity and 77% specificity with a cut off value of 9.9 KpA in adults with NAFLD. However, TE seems to be less efficient in differentiating between F2 and F3 fibrosis.

MRE is an excellent tool for identifying varying degrees of fibrosis in patients with NAFLD.[37,38] Imajo et al[39] showed that MRE is better than TE for identifying fibrosis stage 2 or above, but both the tests are equally sensitive in identifying fibrosis stage 3 or above (i.e., bridging fibrosis). Area under receiver operating characteristics (AUROCs) for TE and MRE were 0.88 and 0.89, respectively. AASLD guidelines recommend MRE and TE for detecting advanced fibrosis in patients with NAFLD.[13]

Another test, like transient elastography, known as shear wave elastography, appears to be less efficient to discriminate between intermediate stages of fibrosis and provide reliable results only in 73% of patients with BMI $\geq$30 kg/m^2.[40]

Indications for liver biopsy

Despite several limitations, liver biopsy is the gold standard for the diagnosis and also for assessing progression and or improvement of histology in NAFLD/NASH.[41] All the guidelines except NICE guideline substantially agree that liver biopsy should not be performed in every NAFLD case to confirm the diagnosis. Guidelines recommend it in the following two situations: (1) uncertain diagnosis and (2) suspected NAFLD-related advanced liver disease.

According to the AASLD guideline liver biopsy is to be performed in patients with metabolic syndrome who are at increased risk of liver inflammation, when other non-invasive scores and imaging suggests the presence of advanced liver fibrosis or when a competing aetiology of liver disease cannot be excluded by other means.[13]

On the other hand, the Asia-Pacific guideline recommends biopsy only when a competing etiology of chronic liver disease cannot be excluded just by laboratory investigations and medical history, or results of noninvasive tests are inconclusive.[10, 11]

Diagnostic algorithms and follow-up strategies

There is no established optimal strategy for following disease progression in patients with NAFLD. The Asia-Pacific guideline proposed the combined use of biochemical tests and imaging studies for reliable evaluation of NAFLD patients.[11] However, they do not specify which noninvasive test is the best. AASLD guideline specifies no diagnostic algorithms or follow-up strategies. AASLD guideline recommends the use of NFS, FIB-4, transient elastography, and MRE as the first-line tests to detect advanced fibrosis in patients with NAFLD.[13]

EASL and Italian guidelines suggest the use of the combination of noninvasive scores (NFS and FIB-4) for assessing presence of significant fibrosis for every patient with NAFLD. Transient elastography should be performed if non-invasive tests are inconclusive. Therefore, in suspected advanced fibrosis, liver biopsy should be performed for final diagnosis.[8,12] NAFLD patients with normal liver enzymes and low risk of advanced fibrosis should undergo non-invasive monitoring of fibrosis in every two years. Patients with evidence of NASH or fibrosis should be screened annually and those with cirrhosis every six months, to perform HCC surveillance.[8,12]

ELF blood tests are proposed to assess the presence of advanced fibrosis in every incidentally detected NAFLD patient by NICE guideline.[9] They also suggest repeating the tests every three years for adults and two years for children if the initial tests are negative. Children and young people with metabolic risk factors or type 2 diabetes mellitus, but without ultrasonic evidence of fatty liver, should be reevaluated every three years.[9]

Treatment of patients with NAFLD

Non-pharmacological treatment

There is no highly-effective pharmacologic treatment for NAFLD. In the absence of effective drug treatment, lifestyle modification, consisting of diet and exercise, remains the cornerstone of therapy for NAFLD. And there is evidence that substantial improvement of liver histology[42,43] occurs with these two measures of diet and exercise.

Life-style changes

All the guidelines advocate lifestyle modification consisting of diet, exercise, and weight loss to treat patients with NAFLD.[8-13] EASL[8], Asia-Pacific[10] and AASLD[13] guidelines advocate the reduction of daily calorie intake by 500–1000 Kcal. AISF position paper[12] recommends daily intake of 1200–1600 Kcal. EASL guideline recommends low-to-moderate fat and moderate-to-high carbohydrate diet. AASLD[13] and NICE[9] guidelines have no specific suggestion regarding dietary composition. In AISF position paper low fat (less than 10% of saturated fatty acid), low carbohydrate diet (<50% of total kcal) is suggested. A Mediterranean diet is recommended as the most effective dietary option to induce a weight loss together. Mediterranean diet also showed beneficial effects on all cardio-metabolic risk factors associated with NAFLD[12]. In Asia-Pacific guideline very low-calorie diets are considered unsustainable, and any specific regimen is preferred over the others.[11]

Allmost all the guidelines recommend exercise (aerobic activities and resistance training) for 150–200 min/wk in 3–5 sessions. A 7–10% weight loss is recommended by all the guidelines as the target of most lifestyle interventions. According to the Asia-Pacific guideline weight loss should be gradual because there is evidence that crash diets have deleterious effect on NASH.[11]

Pharmacological treatment

Indications

According to the EASL guideline[8], pharmacological therapy should be reserved for progressive NASH (bridging fibrosis and cirrhosis); early-stage NASH at high risk for disease progression (age >50 years, metabolic syndrome, diabetes mellitus or increased ALT)[44]; active NASH with high necroinflammatory activities[45]. Similarly, in the AASLD and Asia-Pacific guidelines, drug treatment is recommended only for patients with NASH and fibrosis.[10,13] In the NICE guideline, pharmacological treatment is proposed only for subjects with an advanced liver fibrosis (ELF test >10.51).[9] In the AISF position paper, drug therapy is suggested for patients who are at high risk for disease progression.[12]

Currently, no drugs have been approved for the treatment of NASH by the US Food and Drug Administration or by the European Medicines Agency. All guidelines agree that any medicines prescribed explicitly for NAFLD should be considered as an off-label treatment and that the decision should be discussed with the patient, carefully considering the benefits and the safety. However, the guidelines widely differ in opinion about possibly helpful drugs.

Metformin

Due to the evidence of its limited efficacy in improving the histological features of NAFLD[46-48], metformin is not recommended by any guidelines specifically for treatment of NAFLD[8-13]. However, in a recent meta-analysis it has been shown that treatment of NASH with metformin was associated with normalization of serum aminotransferases in a significantly greater proportion of patients when compared to dietary changes, and hepatic steatosis also improved on imaging.[49]

Peroxisome proliferator-activated receptor (*PPAR*) *agonist*

Treatment with pioglitazone, a PPAR agonist improves insulin sensitivity, aminotransferases, steatosis, inflammation, and ballooning in patients with NASH and prediabetes or T2DM.[50] In PIVENS trial (a large multicenter RCT), pioglitazone improved all histological features (except for fibrosis) and achieved resolution of NASH more often than placebo.[51] The main side effects of glitazones are weight gain[52], and bone fractures in women[53]. According to NICE guideline, pioglitazone should be prescribed only in second and third level centres, after a careful evaluation[9]. In AASLD guideline pioglitazone is recommended only for biopsy-proven NASH[13]. EASL guideline suggests its use for the treatment of

diabetes in patients with a concurrent NAFLD[8]. Asia-Pacific and the Italian guidelines though acknowledge the potential benefits of pioglitazone, suggest that more evidence should be available before a firm recommendation can be made.[11,12]

Antioxidants

In a randomized double-blind placebo-controlled trial (PIVENS trial), daily dose of 800 IU of vitamin E for 96 weeks was found to improve the histological features of NASH (hepatic steatosis, lobular inflammation, and hepatocellular ballooning) in approximately 43% of non-diabetic patients compared with 19% of placebo (p=0.001).[51] Long-term safety of vitamin E is under dispute. NICE[9] and AASLD guidelines[13] (limited to biopsy-proven NASH in the later case) recommend vitamin E. Asia-Pacific guideline does not advocate the use of vitamin E, as current evidence do not found it beneficial.[10] EASL and AISF guidelines are waiting for more evidence before any recommendation. [8, 12]

Incretins

Though in a multicentric randomized placebo-controlled trial, glucagon-like peptide-1 (GLP-1) analogue, liraglutide in patients with biopsy-proven NASH was found to be associated with greater resolution of NASH (relative risk 4.3 [95% CI: 1.0–17.7]; p=0.019) and less progression of fibrosis[54], the guidelines agree that more evidence is required for recommending its use in NASH patients.

Lipid-lowering agents

Despite its hepatotoxic potential, a significant number of NAFLD patients usually receive statins because of their associated cardiovascular risk factors. In a recent review, it is shown that the statins are safe and effective in reducing the associated cardiovascular morbidity in patients with NAFLD, even in patients with slightly elevated alanine transaminases (up to 3 × reference upper limit).[55] All the guidelines agree about the safety of prescribing statins (or continuing an ongoing statin therapy) in patients with NAFLD, even with compensated cirrhosis. But, the guidelines do not recommend routine use of a statin in decompensated cirrhosis and in acute liver failure.[56,57]

Silymarin

A randomised, double-blinded, placebo-controlled study showed the efficacy of silymarin in reducing fibrosis in biopsy-proven NASH.[58] Despite high dose (700 mg three times daily)[58] it was safe and well tolerated. Only Asia-Pacific guideline recommended silymarin as a useful treatment. However, optimal dose and duration still require further studies before a full recommendation.[11]

Ursodeoxycholic acid (UDCA), Omega-3 fatty acids, and miscellaneous agents

AASLD[13] guideline did not recommend the UDCA in patients with NASH/NAFLD because of its non-beneficial role in NASH/NAFLD. EASL[8] guideline did not comment on use of UDCA in patients with NASH. According to AASLD guideline omega-3 fatty acids should not be used as a specific treatment of NAFLD or NASH, but they may be considered to treat hypertriglyceridemia in patients with NAFLD.

Alcohol use in patients with NASH or NAFLD

Heavy alcohol consumption is a risk factor for CLD and should be avoided by patients with NAFLD and NASH according to AASLD guideline.[13] EASL guideline[8] recommends to strictly keep alcohol below the risk threshold (30 gm in men; 20 gm in women).

Agents in registration trials

AASLD guideline[13] recommends that obetocholic acid (OCA) should not be used off-label to treat NASH until further safety and efficacy data become available in patients with NASH. EASL guideline[8] did not comment on OCA.

Bariatric surgery

Bariatric surgery is a useful option for reducing weight and metabolic complications in patients non-responsive to lifestyle changes and pharmacotherapy and the results are stable in the long run.[59] Bariatric surgery improves or eliminates comorbid diseases in most patients and improves long-term survival and death from cardiovascular diseases and malignancy, the two most common causes of death in NAFLD.[13] Bariatric surgery is also found to improve hepatic histology (steatosis, ballooning and fibrosis).[62] But the procedure is associated with peri-operative risk such as higher mortality among patients with compensated cirrhosis (0.9%) and even much higher in those with decompensated cirrhosis (16.3%).[61]

AASLD[13] and EASL[8] guidelines recommend bariatric surgery in patients of NAFLD/NASH unresponsive to lifestyle changes and pharmacotherapy, for reducing weight and metabolic complications. AISF and NICE guidelines put no recommendations regarding bariatric surgery. Asia-Pacific guideline recommended it only for patients with class II obesity (BMI >32.5 kg/m^2 in Asians and 35 kg/m^2 in Caucasians).[11]

Liver transplant (LT)

In Western countries, presently NASH is becoming the most common indication for liver transplant.[62] But post-transplant complications and graft loss are high in NASH patients due to associated obesity, sarcopenia, cardiovascular disease and chronic kidney disease.[63,64] Patients with severe obesity (BMI >40 kg/m^2) may even be considered unfit for liver transplantation because of risk of prolonged ventilation, poor wound healing, higher rate of primary graft non-function, and increased infectious complications.[65] All of the guidelines except AISF and NICE guidelines agree that liver transplantation is an acceptable procedure in NASH patients with an end-stage liver disease. The indications for LT will be same as indications adopted for other etiologies of liver disease.[8-13]

Conclusion

Currently no homogenous management strategy is available for NAFLD. Analysis of recommendations made by the most recent international guidelines for the management of NAFLD show agreement in many points and diversity in some aspects. Most notably the guidelines differ in determining alcohol threshold for defining NAFLD, the screening strategies in high-risk populations, the preferred non-invasive biomarkers for the assessment of advanced fibrosis, and the pharmacological treatment. These differences arise because of geographical variations in genetic predisposition of NAFLD, lifestyle habits and healthcare system. On the other hand, agreement in recommendations of different guidelines could greatly help in ensuring homogenous management of NALFD all over the world, both in clinical practice and in clinical trials. We hope, in future more homogenous guidelines or universal guidelines will be available depending on available evidences. Advancement of imaging technologies and successful clinical trials on potentially effective drugs will help identifying cases of NAFLD/NASH in early stages and will help in better management of these cases.

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