The Diagnosis and Management of Non-alcoholic Fatty Liver Disease: Practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association

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Abbreviations

NAFLD: Nonalcoholic Fatty Liver Disease

NAFL: Nonalcoholic Fatty Liver

NASH: Nonalcoholic Steatohepatitis

T2DM: Type 2 Diabetes Mellitus

AST: Aspartate Aminotransferase

ALT: Alanine Aminotransferase

HOMA: Homeostatic Model Assessment

RCT: Randomized Controlled Trial

PIVENS: Pioglitazone versus Vitamin E versus Placebo for the Treatment of Non-diabetic patients with Nonalcoholic steatohepatitis

TONIC: Treatment of Nonalcoholic Fatty Liver Disease in Children

NAS: NAFLD Activity Score

CK18: Cytokeratin 18 Fragments

ELF: Enhanced Liver Fibrosis Panel

TZD: Thiazolidinediones

UDCA: Ursodeoxycholic Acid

ANA: Anti Nuclear Antibody

ASMA: Anti Smooth Muscle Antibody

US: Ultrasound

CT: Computerized Tomography

MR: Magnetic Resonance

Potential Conflicts of Interest

Naga Chalasani, MD, FACG has received compensation for providing consulting related to NAFLD and NASH from Amylin, Gilead, Genentech, and Mochida and he has received research support from Amylin in the last 3 years. Over the last 3 years, he has received compensation for providing consultation related to drug hepatotoxicity from J & J, Merck, GlaxoSmithKline, Karo Bio, Salix, Advanced Life Sciences, BMS, Teva Pharmaceuticals, Abbott, Biolex, and Vertex.

Zobair Younossi, MD has received consulting fees from Salix, Tibotec, and Vertex.

Anna Mae Diehl, MD has received compensation for providing consulting related to NAFLD from Vertex, Norgine, and Celgene.

Elizabeth Brunt, MD has received compensation from Amylin, Pfizer, and Geneva Foundation for NASH consulting.

Kenneth Cusi, MD has received compensation from Merck, Daichi-Sankyo, and Roche for providing consulting.

Michael Charlton, MD has received compensation from Gilead and Genentech for providing consulting related to NAFLD and NASH.

Joel Lavine, MD, PhD has received compensation for providing consultations related to NAFLD from Quark Pharmaceuticals and Synageva BioPharma, and received research support from Raptor Pharmaceuticals, all in the last 3 years.

Arun Sanyal, MD has served as an ad hoc advisor to Roche, Takeda, Merck, Astella, Sanofi, Exhalenz, and Immuron. He serves as the global PI for trials for Exhalenz and Immuron.

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Preamble

These recommendations are based on the following: (1) a formal review and analysis of the recently published world literature on the topic [Medline search up to June 2011]; (2) the American College of Physicians' *Manual for Assessing Health Practices and Designing Practice Guidelines*;[1] (3) guideline policies of the three societies approving this document; and (4) the experience of the authors and independent reviewers with regards to NAFLD.

Intended for use by physicians and allied health professionals, these recommendations suggest preferred approaches to the diagnostic, therapeutic and preventive aspects of care. They are intended to be flexible and adjustable for individual patients. Specific recommendations are evidence-based wherever possible, and when such evidence is not available or inconsistent, recommendations are made based on the consensus opinion of the authors. To best characterize the evidence cited in support of the recommendations, the AASLD Practice Guidelines Committee has adopted the classification used by the Grading of Recommendation Assessment, Development, and Evaluation (GRADE) workgroup with minor modifications **(Table 1)**.[2] The strength of recommendations in the GRADE system is classified as strong **(1)** or weak **(2)**. The quality of evidence supporting strong or weak recommendations is designated by one of three levels: high **(A)**, moderate **(B)** or low-quality **(C)**.[2] This is a practice guideline for clinicians rather than a review article and interested readers can refer to several comprehensive reviews published recently.[3-8]

Definitions

The definition of nonalcoholic fatty liver disease (NAFLD) requires that (a) there is evidence of hepatic steatosis, either by imaging or by histology and (b) there are no causes for secondary hepatic fat accumulation such as significant alcohol consumption, use of steatogenic medication or hereditary disorders **(Table 2)**. In the majority of patients, NAFLD is associated with metabolic risk factors such as obesity, diabetes mellitus, and dyslipidemia. NAFLD is histologically further categorized into nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH) **(Table 3)**. NAFL is defined as the presence of hepatic steatosis with no evidence of hepatocellular injury in the form of ballooning of the hepatocytes. NASH is defined as the presence of hepatic steatosis and inflammation with hepatocyte injury (ballooning) with or without fibrosis.

Incidence and Prevalence in the General Population

The incidence of NAFLD has been investigated in a limited number of studies. Two Japanese studies[9,10] reported an incidence rate of 31 and 86 cases of suspected NAFLD per 1,000 person-years respectively, whereas another study from England showed a much lower incidence rate of 29 cases per 100,000 person-years.[11] More studies are needed to better understand the incidence of NAFLD across different age, ethnic, and geographic groups.

The reported prevalence of NAFLD varies widely depending on the population studied and the definition used. The prevalence of histologically-defined NAFLD was 20% and 51% in two different studies comprised of potential living liver donors.[12,13] The reported prevalence of NAFLD when defined by liver ultrasound ranged between 17% and 46% depending on the population studied.[4] In a study consisting of nearly 400 middle aged individuals, the prevalence of

NAFLD defined by ultrasonography was 46% and the prevalence of histologically confirmed NASH was 12.2%.[14] In the Dallas Heart Study, when assessed by MR spectroscopy the prevalence of NAFLD in the general population was 31%.[15] The prevalence of suspected NAFLD when estimated using aminotransferases alone without imaging or histology ranged between 7% and 11%, but aminotransferases can be normal in individuals with NAFLD.[4] In summary, estimates of the worldwide prevalence of NAFLD ranges from 6.3% to 33% with a median of 20% in the general population, based on a variety of assessment methods.[4] On the other hand, the estimated prevalence of NASH is lower, ranging from 3 to 5%.[4] The prevalence of NASH cirrhosis in the general population is not known.

Prevalence of NAFLD in High Risk Groups (Table 4)

Obesity is a common and well documented risk factor for NAFLD. Both excessive BMI and visceral obesity are recognized risk factors for NAFLD. In patients with severe obesity undergoing bariatric surgery, the prevalence of NAFLD can exceed 90% and up to 5% of patients may have unsuspected cirrhosis.[4,16-20] There is a very high prevalence of NAFLD in individuals with type 2 diabetes mellitus (T2DM).[4] An ultrasonographic study of patients with T2DM showed a 69% prevalence of NAFLD.[21] In another study, 127 of 204 diabetic patients displayed fatty infiltration on ultrasound, and 87% of the patients with fatty infiltration who consented to biopsy had histologic confirmation of NAFLD.[22] High serum triglyceride levels and low serum HDL levels are very common in patients with NAFLD. The prevalence of NAFLD in individuals with dyslipidemia attending lipid clinics was estimated to be 50%.[23]

Age, gender and ethnicity are also associated with a differential prevalence for NAFLD.[4] A number of studies have shown that the prevalence of NAFLD increases with age.[24-28] The likelihood of disease progression to advanced fibrosis or mortality increases in older patients with NAFLD.[29-31] Many recent studies have reported that male gender is a risk factor for fatty liver disease.[4] For example, in a study of 26,527 subjects undergoing medical checkups, the prevalence of NAFLD was 31% in men and 16% in women.[32] Compared to non-Hispanic whites, Hispanic individuals have significantly higher and non-Hispanic blacks have significantly lower prevalence of NAFLD.[15,33-35] The prevalence of NAFLD in American-Indian and Alaskan-Native populations appears lower, ranging from 0.6% to 2.2%, although the lack of histologic definition makes it likely that is an underestimate.[36,37]

There are data to suggest that hypothyroidism, hypopituitarism, hypogonadism, sleep apnea, and polycystic ovary syndrome independent of obesity are important risk factors for the presence of NAFLD **(Table 4).**[3]

Natural History

The evolution of hepatic histologic changes in patients with NAFL and NASH has been investigated by several studies, but these generally included smaller number of patients and had relatively modest duration of follow-up.[4,7] Nonetheless, it is generally agreed that patients with simple steatosis have very slow, if any, histological progression, while patients with NASH can exhibit histological progression to cirrhotic-stage disease.[4,7]

The long term outcomes of patients with NAFLD and NASH have been reported in several studies.[31, 38-45] Their detailed discussion is beyond the scope of this guideline, but their findings can be summarized as follows; (a) patients with NAFLD have increased overall mortality compared to matched control populations, (b) the most common cause of death in patients with NAFLD, NAFL and NASH is cardiovascular disease, and (c) patients with NASH (but not NAFL) have an increased liver-related mortality rate.

Another piece of indirect evidence that supports the progressive nature of NASH is in the features of cryptogenic cirrhosis which is closely related to NAFLD.[46,47] Patients with cryptogenic cirrhosis have disproportionately high prevalence of metabolic risk factors (T2DM, obesity, metabolic syndrome) typical of patients with NAFLD, their liver biopsies frequently show one or more features of NASH, and studies have demonstrated the loss of histological features of NASH with the development of cirrhosis.[4,7.46,47]

Patients with NAFLD are at increased risk for HCC, but this risk is likely limited to those with advanced fibrosis and cirrhosis.[48-53] Several studies investigated the natural history of NASH cirrhosis in comparison to patients with hepatitis C cirrhosis.[54-57] One large prospective US-based study[55] observed a lower rate of decompensation and mortality in patients with NASH cirrhosis as compared to patients with hepatitis C cirrhosis. However, a more recent international study[56] of 247 NAFLD patients with advanced fibrosis and cirrhosis followed over a mean duration of 85.6 ± 54.5 months showed an overall 10-year survival of 81.5% that was not different from matched patients with hepatitis C cirrhosis. Importantly, both studies have shown that patients with NASH cirrhosis are at significantly lower risk for HCC than patients with hepatitis C cirrhosis.[55,56]

Alcohol Consumption & Definition of NAFLD

By definition, NAFLD indicates the lack of any evidence of ongoing or recent consumption of significant quantities of alcohol. However, the precise definition of significant alcohol consumption in patients with suspected NAFLD is uncertain. A recent consensus meeting[58] concluded that, for NASH clinical trials candidate eligibility purposes, significant alcohol consumption be defined as >21 drinks per week in men and >14 drinks per week in women over a 2-year period prior to baseline liver histology. Furthermore, this group recommended that validated questionnaires should be used to quantify the amount of alcohol consumption in the context of clinical trials. The definition of significant alcohol consumption in the published NAFLD literature has been inconsistent and ranged from > 1 alcoholic drink (~ 10 grams of alcohol per one drink unit) per day to > 40 grams per day, and published studies have not always used gender-specific definitions.[59] If self-reported alcohol consumption details are not consistent with clinical suspicion when evaluating a patient with suspected NAFLD, confirmation with a family member or a close friend should be considered.

Recommendation

1. *Ongoing or recent alcohol consumption > 21 drinks on average per week in men and > 14 drinks on average per week in women is a reasonable definition for significant alcohol consumption when evaluating patients with suspected NAFLD in clinical practice.* ***(Strength – 2, Quality - C)***

Evaluation of Incidentally Discovered Hepatic Steatosis

Some patients undergoing thoracic and abdominal imaging for reasons other than liver symptoms, signs or biochemistry may demonstrate unsuspected hepatic steatosis. While this phenomenon is not uncommon in clinical practice, studies have not systematically examined the characteristics or natural history of NAFLD in this patient population.

Recommendations

2. *In patients with unsuspected hepatic steatosis detected on imaging who have symptoms or signs attributable to liver disease or have abnormal liver biochemistries, they should be evaluated as though they have suspected NAFLD and worked-up accordingly.* ***(Strength – 1, Evidence -A)***
3. *In patients with unsuspected hepatic steatosis detected on imaging who lack any liver-related symptoms or signs and have normal liver biochemistries, it is reasonable to assess for metabolic risk factors (e.g., obesity, glucose intolerance, dyslipidemia) and alternate causes for hepatic steatosis such as significant alcohol consumption or medications.* ***(Strength – 1, Evidence -A)***
4. *In patients with unsuspected hepatic steatosis detected on imaging who are asymptomatic and have normal liver biochemistries, a liver biopsy cannot be recommended..* ***(Strength – 1, Evidence -B)***

Screening in Primary Care, Diabetes, and Obesity Clinics

It can be argued that there should be systematic screening for NAFLD, at least among higher-risk individuals attending diabetes and obesity clinics. However, at present there are significant gaps

in our knowledge regarding the diagnosis, natural history, and treatment of NAFLD. As liver biochemistries can be within normal ranges in patients with NAFLD and NASH, they may not be sufficiently sensitive to serve as screening tests, whereas liver ultrasound is potentially more sensitive but it is expensive and cumbersome as a screening test.

Recommendation

5. *Screening for NAFLD in adults attending primary care clinics or high-risk groups attending diabetes or obesity clinics is not advised at this time due to uncertainties surrounding diagnostic tests and treatment options, along with lack of knowledge related to the long-term benefits and cost-effectiveness of screening.* ***(Strength – 1, Evidence -B)***

Screening of Family Members

Anecdotal experience and some published studies suggest familial clustering and heritability of NAFLD, [60-63] but conclusive studies are lacking. In a retrospective cohort study, Willner et al. observed that 18% of patients with NASH have a similarly affected first degree relative.[60] A small familial aggregation study observed that patients with NAFLD have a significantly higher number of first degree relatives with cirrhosis and a trend towards familial clustering of NAFLD or cryptogenic cirrhosis than matched healthy controls.[62] In another familial aggregation study[63] of overweight children with and without NAFLD, after adjusting for age, gender, race, and BMI, the heritability of MR-measured liver fat fraction was 0.386, and fatty liver was present in 18% of family members of children with NAFLD despite normal ALT and lack of obesity.

Recommendation

6. *Systematic screening of family members for NAFLD is currently not recommended.* ***(Strength – 1, Evidence - B)***

Initial Evaluation

The diagnosis of NAFLD requires that (a) there is hepatic steatosis by imaging or histology, (b) there is no significant alcohol consumption, (c) there are no competing etiologies for hepatic steatosis, and (d) there are no co-existing causes for chronic liver disease.

Common alternative causes of hepatic steatosis are significant alcohol consumption, hepatitis C, medications, parenteral nutrition, Wilson's disease, and severe malnutrition **(Table 2)**. When evaluating a patient with newly suspected NAFLD, it is important to exclude co-existing etiologies for chronic liver disease including hemochromatosis, autoimmune liver disease, chronic viral hepatitis, and Wilson's disease.[3] Mildly elevated serum ferritin is common in patients with NAFLD and it does not necessarily indicate increased iron stores.[3,64] Elevated serum ferritin and transferrin saturation in patients with suspected NAFLD should lead to testing for genetic hemochromatosis. Mutations in the HFE gene occur with variable frequency in patients with NAFLD and their clinical significance is unclear.[64] One should consider a liver biopsy to assess hepatic iron concentration and to exclude significant hepatic injury and fibrosis in a patient with suspected NAFLD with elevated serum ferritin and a homozygote or compound heterozygote C282Y mutation in the HFE gene.[65] Elevated serum autoantibodies are common in patients with NAFLD and are generally considered to be an epiphenomenon.[3] In a recently published large study from the NASH Clinical Research Network, positive serum autoantibodies, defined as ANA > 1:160 or ASMA >1:40 were present in 21% of patients with well-phenotyped NAFLD and were not associated with more advanced histologic features.[66]

Recommendations

7. *When evaluating a patient with suspected NAFLD, it is essential to exclude competing etiologies for steatosis and co-existing common chronic liver disease.* ***(Strength – 1, Evidence - A)***
8. *Persistently high serum ferritin and increased iron saturation, especially in the context of homozygote or heterozygote C282Y HFE mutations may warrant a liver biopsy.* ***(Strength – 1, Evidence - B)***
9. *High serum titers of autoantibodies in association with other features suggestive of autoimmune liver disease (very high aminotransferases, high globulin) should prompt a more complete work-up for autoimmune liver disease.* ***(Strength – 1, Evidence - B)***

Non-invasive assessment of steatohepatitis and advanced fibrosis in NAFLD

The natural history of NAFLD is fairly dichotomous – NAFL is generally benign whereas NASH can progress to cirrhosis, liver failure, and liver cancer. Existing dogma posits that liver biopsy is the most reliable approach for identifying the presence of steatohepatitis and fibrosis in patients with NAFLD, but it is generally acknowledged that biopsy is limited by cost, sampling error, and procedure-related morbidity and mortality. Serum aminotransferase levels and imaging tests such as ultrasound, CT, and MR do not reliably assess steatohepatitis and fibrosis in patients with NAFLD. Therefore, there has been significant interest in developing clinical prediction rules and non-invasive biomarkers for identifying steatohepatitis in patients with NAFLD,[7] but their detailed discussion is beyond the scope of this practice guideline.

The presence of metabolic syndrome is a strong predictor for the presence of steatohepatitis in patients with NAFLD[3,7,67-69] and may be used to best identify patients with persistently abnormal liver biochemistries who would benefit diagnostically and prognostically from a liver biopsy.

There has been intense interest in non-invasive methods to identify advanced fibrosis in patients with NAFLD.[7];these include the NAFLD Fibrosis Score[70], Enhanced Liver Fibrosis (ELF) panel[70] and transient elastography. The NAFLD Fibrosis Score is based on six readily available variables (age, BMI, hyperglycemia, platelet count, albumin, AST/ALT ratio) and it is calculated using the published formula *(http://nafldscore.com*). In a meta-analysis of 13 studies consisting of 3,064 patients,[7] NAFLD Fibrosis Score has an AUROC of 0.85 for predicting advanced fibrosis (i.e., bridging fibrosis or cirrhosis) and a score < -1.455 had 90% sensitivity and 60% specificity to exclude advanced fibrosis whereas a score > 0.676 had 67% sensitivity and 97% specificity to identify the presence of advanced fibrosis. The ELF panel consists of plasma levels of three matrix turnover proteins (hyaluronic acid, TIMP-1, and PIIINP) had an AUROC of 0.90 with 80% sensitivity and 90% specificity for detecting advanced fibrosis.[71] This panel has been recently approved for commercial use in Europe, but is not available in the United States.

Circulating levels of cytokeratin-18 (CK18) fragments have been investigated extensively as novel biomarkers for the presence of steatohepatitis in patients with NAFLD.[7] Feldstein *et al.*, measured CK18 fragments in plasma that had been obtained from 44 consecutive patients with suspected NAFLD at the time of liver biopsy, and correlated the findings with hepatic immunohistochemistry data.[72] Plasma CK18 fragments were markedly increased in patients with NASH compared with patients with simple steatosis or normal biopsies (median 765.7 U/L versus

202.4 U/L or 215.5 U/L, respectively; P < .001), and independently predicted NASH (OR 1.95; 95% CI 1.18-3.22 for every 50 U/L increase). This observation was reproduced in several subsequent studies and a recent meta-analysis estimated that plasma CK18 levels have a sensitivity of 78%, specificity of 87%, and an area under the receiver operating curve (AUROC) of 0.82 (95% CI: 0.78-0.88) for steatohepatitis in patients with NAFLD.[7] Although these are very encouraging results, currently this assay is not commercially available. Furthermore, as each study utilized a study-specific cut-off value, there is not an established cut-off value for identifying steatohepatitis.

Transient elastography, which measures liver stiffness non-invasively, has been successful in identifying advanced fibrosis in patients with hepatitis B and hepatitis C. Although a recent meta-analysis showed high sensitivity and specificity for identifying fibrosis in NAFLD,[7] it has a high failure rate in individuals with a higher BMI. Furthermore, it is not commercially available in the United States. Other imaging tools such as MR elastography are currently research tools.

A major limitation of these prediction models and biomarkers is that they have largely been investigated in cross-sectional studies and thus their utility in monitoring disease natural history, predicting outcomes or response to therapeutic intervention is unknown.

Recommendations

10. As the metabolic syndrome predicts the presence of steatohepatitis in patients with NAFLD, its presence can be used to target patients for a liver biopsy. ***(Strength – 1, Evidence - B)***

11. NAFLD Fibrosis Score is a clinically useful tool for identifying NAFLD patients with higher likelihood of having bridging fibrosis and/or cirrhosis. ***(Strength – 1, Evidence - B)***

12. Although serum/plasma CK18 is a promising biomarker for identifying steatohepatitis, it is premature to recommend in routine clinical practice. ***(Strength – 1, Evidence - B)***

When to obtain a liver biopsy in patients with NAFLD?

Liver biopsy remains the gold standard for characterizing liver histology in patients with NAFLD. However, it is expensive and carries some morbidity and very rare mortality risk. Thus, it should be performed in those who would benefit the most from diagnostic, therapeutic guidance, and prognostic perspectives.

Recommendations

13. Liver biopsy should be considered in patients with NAFLD who are at increased risk to have steatohepatitis and advanced fibrosis. ***(Strength – 1, Evidence - B)***

14. The presence of metabolic syndrome and the NAFLD Fibrosis Score may be used for identifying patients who are at risk for steatohepatitis and advanced fibrosis. ***(Strength – 1, Evidence - B)***

15. Liver biopsy should be considered in patients with suspected NAFLD in whom competing etiologies for hepatic steatosis and co-existing chronic liver diseases cannot be excluded without a liver biopsy. ***(Strength – 1, Evidence - B)***

MANAGEMENT OF PATIENTS WITH NAFLD

The management of patients with NAFLD consists of treating liver disease as well as the associated metabolic co-morbidities such as obesity, hyperlipidemia, insulin resistance and

T2DM. As patients with NAFLD without steatohepatitis have excellent prognosis from a liver standpoint, treatments aimed at improving liver disease should be limited to those with NASH.

Lifestyle intervention

Many studies indicate that lifestyle modification may reduce aminotransferases and improve hepatic steatosis when measured either by ultrasound[73-80] or MR imaging and spectroscopy.[81-94] In a meta-analysis of 15 early case series and clinical studies spanning between 1967 through 2000, most studies reported reductions in aminotransferases and hepatic steatosis by ultrasound across a broad spectrum of diets of different caloric restriction intensities and macronutrient composition (low *vs.* high carbohydrate, low *vs.* high fat, saturated *vs.* unsaturated fat diets).[95] However, these early studies were inconclusive as a result of being small, largely uncontrolled and few using histology as the primary endpoint. More recent uncontrolled studies also showed an improvement in aminotransferases and hepatic steatosis on histology with lifestyle modification.[96-98]

Orlistat (an enteric lipase inhibitor) in conjunction with lifestyle modification was investigated in two randomized controlled trials. In the study by Ziegler-Sagi *et al.*,[99] orlistat reportedly improved ALT and steatosis by US, but its effect on liver histology could not be evaluated because the majority of patients did not undergo a follow-up liver biopsy. However, in the study by Harrison *et al.*,[100] orlistat did not improve body weight or liver histology.

The best evidence for weight loss as a means to improve liver histology in NASH comes from a trial that randomized 31 obese persons with NASH to intensive lifestyle changes (diet, behaviour modification and 200 minutes a week of moderate physical activity for 48 weeks) versus structured basic education alone.[101] The intensive arm had 9.3% weight loss (versus 0.2% in the

dietary counseling alone arm) and led to an improvement in steatosis, necrosis and inflammation, but not fibrosis. Importantly, participants with ≥ 7% weight loss had significant improvement in steatosis, lobular inflammation, ballooning, and NAFLD Activity Score (NAS).[101] There was a similar pattern in the study by Harrison *et al.*,[100] where participants who lost > 5% body weight improved steatosis, whereas individuals with ≥ 9% weight loss had significant improvement in steatosis, lobular inflammation, ballooning, and NAS.

A number of recent studies used MR spectroscopy to assess changes in hepatic fat in response to lifestyle modification. The results from these studies using a variety of interventions, either by diet alone[81, 83, 84, 89, 92, 93] or in combination with different exercise prescriptions,[82,85-88,92,94] have consistently reported a significant reduction in liver fat by an average of ~40% (ranging from 20% to 81%). The degree of hepatic fat reduction was proportional to the intensity of the lifestyle intervention and generally required a body weight loss between ~5 to 10%.[82.88,92]

The effect of exercise without dietary modification on hepatic steatosis was investigated in four studies using MR spectroscopy.[102-105] Exercise programs consisted of 2-3 sessions a week of 30-60 minutes over a period of 6 to 12 weeks. In all but one study[101] liver fat content diminished without a significant change in body weight.

Recommendations

16. Weight loss generally reduces hepatic steatosis, achieved either by hypocaloric diet alone or in conjunction with increased physical activity. ***(Strength – 1, Evidence - A)***

17. Loss of at least 3-5% of body weight appears necessary to improve steatosis, but a greater

weight loss (up to 10%) may be needed to improve necroinflammation. ***(Strength – 1, Evidence - B)***

18. Exercise alone in adults with NAFLD may reduce hepatic steatosis but its ability to improve other aspects of liver histology remains unknown. ***(Strength – 1, Evidence - B)***

INSULIN SENSITIZING AGENTS

Metformin

Several studies investigated the effect of metformin on aminotransferases and liver histology in patients with NASH. Early small, open-label studies demonstrated a reduction in insulin resistance and aminotransferases[106-108] but no significant improvement in liver histology.[107,108] An open-label trial consisting of 110 patients with NASH received either metformin 2 grams/day (55 patients), vitamin E 800 IU/day (28 patients) or dietary-induced weight loss (27 patients) for 12 months.[109] Aminotransferases improved more with metformin than with vitamin E or diet alone. However, there was only a modest improvement in hepatic steatosis and inflammation in the subset of 17 patients undergoing paired liver biopsies with metformin treatment. In a 48-week open-label study in 26 patients, metformin improved NASH activity in only 30% of patients, although interpretation of the study was confounded by a significant weight loss in the responders (19% lost more than 10 kilograms).[110] Haukeland *et al.*[111] reported a similar lack of efficacy in a larger (n=48) randomized control trial (RCT) of metformin *vs*. placebo with a similar dietary and exercise intervention in both groups. Other studies also failed to show major benefit for metformin on hepatic insulin sensitivity, aminotransferases[111-116] or liver histology.[111,113,116] A recent meta-analysis[4] concluded that 6-12 months of metformin plus lifestyle intervention did not improve aminotransferases or liver histology, compared with lifestyle intervention alone,

independently of metformin dose or the presence of diabetes.

Recommendation

19. Metformin has no significant effect on liver histology and is not recommended as a specific treatment for liver disease in adults with NASH. ***(Strength – 1, Evidence - A)***

Thiazolidinediones

Several studies investigated the effect of pioglitazone and rosiglitazone on aminotransferases and liver histology in adults with NASH. In an early uncontrolled open-label study[117] in 22 subjects with biopsy-proven NASH, rosiglitazone improved aminotransferases and hepatic steatosis, ballooning and inflammation scores, but not fibrosis. But in a subsequent RCT, Ratziu *et al.*[118] observed that rosiglitazone improved aminotransferases and hepatic steatosis, but not necroinflammation or fibrosis and its two-year open-label extension phase also showed similar results.[119] Belfort *et al.*[120] conducted a RCT of pioglitazone (45 mg/day) in patients with NASH who had impaired glucose tolerance or T2DM. Although there was a significant weight gain (2.5 ± 0.5 kg) with pioglitazone, it significantly improved aminotransferases, steatosis, ballooning, and inflammation. The NAS improved with pioglitazone in 73% compared to 24% of placebo-treated patients ($p<0.001$) and there was a trend towards improvement in fibrosis among patients randomized to pioglitazone ($p=0.08$). Aithal *et al.*[121] performed a RCT of lifestyle intervention with either pioglitazone 30 mg/day or placebo for 12 months in a total of 74 patients with NASH. While steatosis did not improve significantly compared to placebo, hepatocellular injury and fibrosis improved significantly.[1210] The PIVENS[122] study is a large multicenter RCT that randomized 247 non-diabetic patients with NASH to pioglitazone (30 mg/day), vitamin E (800 IU/day), or placebo for 24 months. The primary endpoint was an improvement in NAS ≥ 2 points

with at least 1 point improvement in hepatocellular ballooning and 1-point improvement in either the lobular inflammation or steatosis score, and no increase in the fibrosis score.[122] It was achieved in 19% in the placebo group compared to 34% in the pioglitazone group (p=0.04 *vs.* placebo) and 43% in the vitamin E group (p=0.001 *vs.* placebo).[122] Because this study consisted of two primary comparisons (pioglitazone *vs.* placebo and vitamin E *vs.* placebo), a p-value of 0.025 was considered to be significant ***a priori.*** Therefore, although there were histological benefits associated with pioglitazone, this study concluded that pioglitazone did not meet the primary end point. However, resolution of NASH, a key secondary end point, was achieved in significantly higher number of patients receiving pioglitazone than receiving placebo (47% *vs.* 21%, p=0.001).[122] Of note, pioglitazone was associated with a 4.7 kg weight gain compared to placebo (p<0.001). Vitamin E and pioglitazone were well tolerated and there were no differences in other adverse events.

A recent meta-analysis[4] that included 5 RCTs showed that pioglitazone significantly improved steatosis (OR 4.05, 95% CI 2.58-6.35) and inflammation (OR 3.53, 95% CI 2.21-5.64), but not fibrosis (OR 1.40, 95% CI 0.87-2.24).

There has been considerable debate about the long-term safety of TZDs regarding cardiovascular disease, congestive heart failure (CHF), bladder cancer, and bone loss. In a recent meta-analysis[123] of 19 trials enrolling a total of 16,390 patients with T2DM, pioglitazone treatment was associated with a significant reduction (~18%) in the primary outcome of death, myocardial infarction, or stroke (p=0.005). However, there was also a higher rate of CHF with pioglitazone (2.3% vs. 1.8% in the control group, p=0.002), so caution must be exercised when considering its use in patients with impaired myocardial function. Due to increased risk of

coronary events, rosiglitazone is no longer marketed in Europe and its use is highly restricted in the United States.

Recommendation

20. Pioglitazone can be used to treat steatohepatitis in patients with biopsy-proven NASH. However, it should be noted that majority of the patients who participated in clinical trials that investigated pioglitazone for NASH were non-diabetic and that long term safety and efficacy of pioglitazone in patients with NASH is not established. ***(Strength – 1, Evidence - B)***

Vitamin E

Oxidative stress is considered to be a key mechanism of hepatocellular injury and disease progression in subjects with NASH. Vitamin E is an anti-oxidant and has been investigated to treat NASH.[124-128] Comparison between these trials is difficult due to varying criteria for entry into the study, different doses of vitamin E and unclear formulations of vitamin E used which could affect its bioavailability, the additional use of other anti-oxidants or other drugs and limited histologic data to assess outcomes. Also, most studies were relatively under-powered and did not meet or publish CONSORT criteria for clinical trials. Despite these limitations, it can be summarized that (1) the use of vitamin E is associated with a decrease in aminotransferases in subjects with NASH, (2) studies where histologic endpoints were evaluated indicate that vitamin E causes improvement in steatosis, inflammation, and ballooning and resolution of steatohepatitis in adults with NASH, and (3) vitamin E has no effect on hepatic fibrosis. Although two meta-analyses[8,129] failed to observe significant histological benefits with vitamin E in patients with NASH, these analyses were conducted before PIVENS[122] and TONIC[130] trials were published. In the largest clinical trial (PIVENS)[122] reported to date, the pure form of rrr α-tocopherol was orally

administered at a dose of 800 IU/day for 96 weeks. The primary endpoint as stated previously was achieved in a significantly greater number of participants receiving vitamin E compared to placebo (42% *vs*. 19%, p< 0.001, number needed to treat= 4.4). .

One concern with vitamin E is the controversial issue of whether it increases all-cause mortality. Some meta-analyses have reported an increase in all-cause mortality with high dose vitamin E,[131,132] but others failed to confirm such an association.[133-135] A recently published RCT showed that vitamin E administered at a dose of 400 IU/day increased the risk of prostate cancer in relatively healthy men (absolute increase of 1.6 per 1000 person years of vitamin E use).[136]

Recommendation

21. Vitamin E (α-tocopherol) administered at daily dose of 800 IU/day improves liver histology in non-diabetic adults with biopsy-proven NASH and therefore it should be considered as a first-line pharmacotherapy for this patient population. ***(1B)***

22. Until further data supporting its effectiveness become available, vitamin E is not recommended to treat NASH in diabetic patients, NAFLD without liver biopsy, NASH cirrhosis, or cryptogenic cirrhosis ***(1C)***

Ursodeoxycholic acid (UDCA), Omega-3 fatty acids, and Miscellaneous Agents

Several studies[126,137-140] investigated UDCA (conventional and high doses) to improve aminotransferases and steatosis in patients with NAFLD and liver histology in patients with NASH. All but one study[139] have been proof-of-concept studies with small number of participants and/or surrogate endpoints. Notably, a single large multicenter RCT convincingly showed that UDCA offers no histological benefit over placebo in patients with NASH.[139] Omega-3 fatty acids, currently approved in the United States to treat hypertriglyceridemia, have been

investigated to treat NAFLD both in animal models and in humans.[141] A recent review by Masterton *et al*,[142] of published literature related to omega-3 fatty acids in NAFLD , found experimental evidence to support their use but the interpretation of human studies were limited by small sample size and methodological flaws. A large multicenter study of one omega-3 fatty acid (eicosapentanoic acid) to treat NASH is ongoing in the United States.. More than a dozen other miscellaneous agents have been investigated in small, proof-of-concept studies and their detailed evaluation is beyond the scope of this guideline

Recommendations

23. UDCA is not recommended for the treatment of NAFLD or NASH. ***(Strength – 1, Quality – B)***

24. It is premature to recommend omega-3 fatty acids for the specific treatment of NAFLD or NASH but they may be considered as the first line agents to treat hypertriglyceridemia in patients with NAFLD. ***(Strength – 1, Quality – B)***

Bariatric Surgery

As the majority of patients undergoing bariatric surgery have associated fatty liver disease, there has been an interest in foregut bariatric surgery as a potential treatment option for NASH. There are no RCTs that evaluated any type of foregut bariatric surgical procedure to specifically treat NAFLD or NASH. However, there are several retrospective and prospective cohort studies that compared liver histology in the severely obese individuals before and after bariatric surgery. Unfortunately, in the majority of these studies, post-bypass liver biopsies were performed at varying intervals and only in selected patients undergoing surgical procedures such as hernia

repair or adhesiolysis. One exception is the study by Mathurin *et al.*,[143] that prospectively correlated clinical and metabolic data with liver histology before and 1 and 5 years after bariatric surgery in 381 adult patients with severe obesity. Gastric band, bilio-intestinal bypass, and gastric bypass were done in 56%, 23%, and 21%, respectively. Compared to baseline, there was a significant improvement in the prevalence and severity of steatosis and ballooning at 1 and 5 years following bariatric surgery. In patients with probable or definite NASH at baseline (n=99), there was a significant improvement in steatosis, ballooning, and NAS and resolution of probable or definite NASH at 1 and 5 years following bariatric surgery. Most histological benefits were evident at 1 year with no differences in liver histology between 1 and 5 years following bariatric surgery. Intriguingly, a minor but statistically significant increase in mean fibrosis score was noted at 5 years after the bariatric surgery (from 0.27± 0.55 at baseline to 0.36 ± 0.59, p=0.001). Despite this increase, at 5 years 96% of patients exhibited fibrosis score ≤ F1 and 0.5% had F3, indicating there is no clinically significant worsening in fibrosis that can be attributed directly to the procedure. In the important subgroup of patients with probable or definite NASH at baseline, there was no worsening of fibrosis at 1 and 5 years, compared to baseline liver biopsy. As no patient in the study had F3 or F4 at baseline, the effect of bariatric surgery in those with advanced fibrosis and cirrhosis could not be evaluated.

Two meta-analyses[144,145] evaluated the effect of bariatric surgery on the liver histology in patients with NAFLD. The meta-analysis by Mummadi *et al.*,[144] showed that steatosis, steatohepatitis, and fibrosis appear to improve or completely resolve after bariatric surgery. However, a recently published Cochrane review[145] concluded that lack of randomized clinical trials or quasi-

randomized clinical studies prevents definitive assessment of benefits and harms of bariatric surgery as a therapeutic approach for patients with NASH.

Recommendations

25. *Foregut bariatric surgery is not contraindicated in otherwise eligible obese individuals with NAFLD or NASH (but without established cirrhosis).* ***(Strength – 1, Quality – A)***
26. *The type, safety and efficacy of foregut bariatric surgery in otherwise eligible obese individuals with established cirrhosis due to NAFLD are not established.* ***(Strength – 1, Quality – B)***
27. *It is premature to consider foregut bariatric surgery as an established option to specifically treat NASH* ***(1B)***

Alcohol use in patients with NAFLD and NASH

Heavy alcohol consumption is a risk factor for chronic liver disease and should be avoided by patients with NAFLD and NASH. The National Institute on Alcohol Abuse and Alcoholism (NIAAA) defines heavy or at-risk drinking as more than 4 drinks on any day or more than 14 drinks per week in men or more than 3 drinks on any day on 7 drinks per week in women.[146] Several recent cross-sectional studies[147-153] suggest a beneficial effect of light alcohol consumption (on average less than one drink per day) on the presence (defined either biochemically or by imaging) and severity of NAFLD. There are no studies reporting the effect of ongoing alcohol consumption on disease severity or natural history of NAFLD or NASH. The effects of light drinking on the cardiovascular system and cancer risks, if any, have not been investigated in individuals with NAFLD.

Recommendations

28. *Patients with NAFLD should not consume heavy amounts of alcohol* ***(Strength -1, Quality – B)***
29. *No recommendation can be made with regards to non-heavy consumption of alcohol by individuals with NAFLD.* ***(Strength – 1, Quality – B)***

Statin use in patients with NAFLD and NASH

Patients with NAFLD and NASH are at increased risk for cardiovascular disease and several studies have established cardiovascular disease as their most common cause of death.[6] Patients with NAFLD should be risk stratified for cardiovascular disease, and their cardiovascular risk factors should be managed accordingly.[154] The treatment of dyslipidemia should be considered in the overall frame work of cardiovascular risk reduction in patients with NAFLD.[154]

Statins are an important class of agents to treat dyslipidemia, and yet there is continued reluctance to use statins in patients with suspected or established chronic liver disease, including NAFLD and NASH. Although elevated aminotransferases are not uncommon in patients receiving statins, serious liver injury from statins is rarely seen in clinical practice. Over the last decade, one RCT and several retrospective and prospective studies[155-159] have established that (a) statins are safe in patients with liver disease and (b) there is no evidence that patients with chronic liver disease including at NAFLD and NASH are at higher risk for serious liver injury from statins than those without liver disease.

Several studies have suggested that statins may improve liver biochemistries and histology in patients with NASH.[159-167] These studies consisted of small number of patients and have not been rigorously designed. A recent *post-hoc* analysis of the cardiovascular outcomes study, GREACE,[165] observed that statins significantly improve liver biochemistries and cardiovascular outcomes in patients with elevated liver enzymes likely due to NAFLD. There are no RCTs with histological endpoints which investigated statins to treat NASH.

Recommendations

30. Given the lack of evidence to show that patients with NAFLD and NASH are at increased risk for serious drug-induced liver injury from statins, statins can be used to treat dyslipidemia in patients with NAFLD and NASH. ***(Strength – 1, Quality – B)***

31. Until RCTs with histological endpoints prove their efficacy, statins should not be used to specifically treat NASH. ***(Strength – 1, Quality – B)***

NAFLD in patients with other chronic liver diseases

Because of the high prevalence of risk factors for NAFLD and NASH, it is not uncommon for patients with other chronic liver diseases to exhibit co-existing histological features of NAFLD.[168] Coexistent hepatic steatosis is common in chronic hepatitis C (HCV) infection and is strongly associated with more advanced liver disease.[169-171] Another large study showed high prevalence of steatosis (40.5%) and steatohepatitis (15%) in patients with primary biliary cirrhosis (PBC),[172] although at least some of the steatosis and steatohepatitis in that study was suspected to be due to alcohol consumption. In clinical practice, it is not uncommon for obese and/or diabetic patients with autoimmune liver disease to exhibit steatosis and steatohepatitis in their liver biopsies.

Previous studies have shown that obesity, insulin resistance, and hepatic steatosis are associated with a lower response to pegylated interferon and ribavirin for the treatment of HCV.[173-175] Obesity does not have a similar negative impact on the response to newer protease-inhibitor based anti-viral regimens,[176-180] but the impact of insulin resistance and hepatic steatosis has not yet been investigated sufficiently. It is not known if the treatment of steatosis and steatohepatitis alters the natural history of other chronic liver diseases such as HCV and PBC. Furthermore, it is not known if agents such as vitamin E and pioglitazone are effective to treat steatosis and steatohepatitis when present in patients with other chronic liver diseases.

Recommendations

32. *When steatosis and steatohepatitis are evident in patients with other types of chronic liver disease, it is important to assess for metabolic risk factors and alternate etiologies for hepatic steatosis.* ***(Strength – 1, Quality – B)***
33. *In patients with other types of chronic liver diseases who have co-existing NAFLD and NASH, there are no data to support the use of vitamin E or pioglitazone to improve the liver disease.* ***(Strength – 1, Quality – B)***

Miscellaneous Recommendations Pertinent to Clinical Practice

34. *Patients with NASH cirrhosis should be screened for gastroesophageal varices according to the AASLD/ACG practice guidelines.*[181] ***(Strength – 1, Quality – B)***
35. *Patients with NASH cirrhosis should be considered for HCC screening according to the AASLD/ACG practice guidelines.*[182] ***(Strength – 1, Quality – B)***

36. Current evidence does not support routinely repeating a liver biopsy in patients with NAFL or NASH. **(*Strength – 2, Quality – C*)**

Aspects of NAFLD Specific to Children and Adolescents

Recognition of NAFLD in children is essential to understanding the origin of disease in those likely to be most genetically or environmentally susceptible. Adults with onset of NAFLD in childhood may be most at risk for early or severe complications. Definition of NAFLD in childhood is the same as in adults. Children are reported with NAFLD as early as 2 years and with NASH-related cirrhosis as early as age 8.[183,184]

Prevalence and Risk Factors

Estimation of population prevalence in children presents difficulties for the same reasons detailed above in adults. Estimates vary based upon the type of test or imaging, the cut-points for detection, and the age, sex, race and ethnicity of the geographic region sampled. A school-based study of obese children in Minnesota, California, Texas and Louisiana, using abnormal serum ALT as a surrogate marker (>40U/L), found that 23% of 17-18 year olds had elevated unexplained ALT.[183] An autopsy study using the "gold standard" of liver histology examined 742 children between the ages of 2-19 y who died from unnatural causes. The estimated NAFLD prevalence was 9.6% when adjusted for age, gender, race and ethnicity.[184] Multivariate analyses showed that obesity, older age (in adolescence), male gender, and Hispanic ethnicity are independent predictors of fatty liver prevalence.

Natural History of NAFLD in Children

A single retrospective single center report has been published on the natural history of NAFLD in 66 children.[185] Only 5 had serial biopsies, obtained for unspecified reasons over varying intervals, averaging 41 months between biopsies. Of these 5 children, 4 had progression of fibrosis. Four of the 5 underwent liver transplantation and 2 died of cirrhosis. Clearly, more robust prospective data are needed on larger number of children to better understand the natural history of NAFLD in children.

Screening for NAFLD in Children

NAFLD is under-diagnosed in children due to lack of recognition, screening or appreciation of associated complications by health care providers. One study showed that less than a third of obese children were screened for NAFLD at clinic visits.[186] Children may not be recognized as obese at visits and age-appropriate norms for body mass index may go unacknowledged. Abdominal adiposity may mask detection of hepatomegaly by palpation during physician examination. As in adults, children with features of metabolic syndrome such as obesity, hypertension, insulin resistance and dyslipidemia[187] are at higher risk for NAFLD and particular histopathological features of NAFLD correlate with components of metabolic syndrome.[188] Thus, identification of children at risk for NAFLD could occur in general health provider settings as well as in specialty clinics for nutrition, gastroenterology, hepatology, endocrinology and bariatric surgery. Children may also exhibit NAFLD incidentally discovered while undergoing imaging, but there are no studies evaluating how to proceed with children identified in this fashion. Recently, the summary report of an expert committee suggested biannual screening for liver disease with serum ALT and AST starting at age 10 years in obese children and those with BMI of 85th to 94th percentile with other risk factors.[189]

Penetrance of NAFLD has been demonstrated in family members of children with NAFLD.[63] The likelihood of first, second and third degree relatives exhibiting abnormally high fat fractions (by MRI estimation) relative to body mass index is much more highly correlated in those related to a child with NAFLD than to those who are related to an age, gender and BMI-matched child without NAFLD.

Diagnosis in children

Given the relatively early onset, caregivers must give additional consideration to the possibility of monogenic disorders that present as fatty liver disease in very young children. Considerations include inborn errors of fatty acid or carnitine metabolism, peroxisomal disorders, lysosomal storage disorders, Wilson's disease, and cystic fibrosis.[190] However, as in adults, positive serum autoantibodies are present in a significant population of children with biopsy-proven NAFLD and on some occasion liver biopsy is required to discriminate between autoimmune hepatitis and NAFLD.[187] Obviously, the confounding factor of alcoholism is much less common in children and standard questionnaires for quantifying alcohol intake are usually unnecessary.

Recommendations

37. Children with fatty liver who are very young or not overweight should be tested for monogenic causes of chronic liver disease such as fatty acid oxidation defects, lysosomal storage diseases and peroxisomal disorders, in addition to those causes considered for adults. ***(Strength – 2, Quality – C)***

38. *Low serum titers of autoantibodies are often present in children with NAFLD, but higher titers, particularly in association with higher serum aminotransferases and high globulin should prompt a liver biopsy to evaluate for possible autoimmune hepatitis.* ***(Strength – 2, Quality – B)***
39. *Due to a paucity of evidence, a formal recommendation cannot be made with regards to screening for NAFLD in overweight and obese children despite a recent expert committee recommendation for biannual screening for liver disease with liver enzyme measurements in this population.* ***(Strength –1, Quality – B).***

When to obtain a liver biopsy for suspected pediatric NAFLD?

The decision to perform a liver biopsy in a child to confirm the diagnosis of NAFLD must be weighed against the risks associated with biopsy and the likelihood that the result will impact management. In children with an uncertain diagnosis, biopsy may rule out potential drug hepatotoxicity or lack of clarity due to presence of serum autoantibodies. When there is an interest in grading or staging NAFLD, instead of submitting all children with NAFLD to a liver biopsy it would be optimal to identify those children who are more likely to have NASH. The paucity of natural history data confounds the decision to biopsy since alteration of long-term outcomes with treatment based on severity of histology at baseline is unknown.

As in adults, development of noninvasive biomarkers or imaging to identify those at risk for more rapid progression or severe disease onset is desirable. Particularly, accurate markers of cellular injury and fibrosis are needed. Two studies suggested that ELF score can be used to accurately predict fibrosis in children with NAFLD, but both studies consisted of relatively small number of

children and fewer with advanced fibrosis.[191,192] There is reported benefit in predicting fibrosis stage in pediatric patients, with a AUROC of 0.92, although only 9 of the 76 subjects studied had fibrosis stage 3 or more.[190] Validation of the serum CK18 levels to evaluate NASH needs to be undertaken in children with NAFLD.

Recommendations

40. Liver biopsy in children with suspected NAFLD should be performed in those where the diagnosis is unclear, where there is possibility of multiple diagnoses, or before starting therapy with potentially hepatotoxic medications. ***(Strength – 1, Quality – B)***

41. A liver biopsy to establish a diagnosis of NASH should be obtained prior to starting children on pharmacologic therapy for NASH. ***(Strength – 2, Quality – C)***

NAFLD Histology in Children

Histopathology of children with NAFLD can differ from that found in adults.[192] As in adults, children can present with pronounced features of hepatocellular injury, lobular inflammation, and peri-sinusoidal fibrosis, but there is a unique pattern of unclear significance also recognized in children. This pattern is typified by marked macrovesicular hepatocellular steatosis, portal inflammation and portal fibrosis in the absence of ballooning.[183,194,195]

Recommendation:

42. Pathologists interpreting pediatric NAFLD biopsies should recognize the unique pattern frequently found in children to not misidentify pediatric NAFLD. ***(Strength – 1, Quality – B)***

Treatment in Children

Recommendations for pediatric treatment options are limited by a small number of randomized clinical trials and insufficient information on natural history to assess risk-benefit. The overall goal is to improve a child's quality of life and reduce longer term cardiovascular and liver morbidity and mortality. Given that early-onset likely indicates higher likelihood of later complications, attempts should be made to identify children who will benefit from intervention.

Lifestyle modification

Since most pediatric NAFLD patients are obese, addressing their obesity is the first step. An open label study [196] in 84 Italian children with biopsy-proven NAFLD showed that >20% body weight reduction over 12 months resulted in improvement in serum ALT and steatosis by ultrasonography in most children with NAFLD. Reportedly, 94% of the 70 enrolled subjects were able to achieve this weight loss goal using caloric restriction and exercise advice. Since liver biopsies were not performed at the end of the study, the effect of lifestyle intervention on liver histology could not be determined. In another study, Nobili *et al.*[197] randomized 53 children with biopsy-proven NAFLD to lifestyle modification plus antioxidant therapy or lifestyle modification and placebo. Antioxidant therapy did not improve liver histology, but children in both groups showed significant improvement in steatosis, inflammation, ballooning, and the NAS. Although there are no randomized controlled trials of intensive lifestyle modification compared to standard-of-care advice, two studies [196,197] indicate that lifestyle modification is beneficial in children with NAFLD.

No information exists on recommending any particular type of diet or exercise. Further studies are needed to assess the efficacy of specific diets. Recommendations for overweight pediatric

NAFLD patients should include consultation with a registered dietitian to assess quality of diet and measurement of caloric intake, adoption of American Heart Association dietary strategies, and regular aerobic exercise progressing in difficulty as fitness allows.[198] Enlisting other willing family members to adopt diet and exercise goals may aid compliance.

Pharmacotherapy

As in adults, clinical trials for pediatric NAFLD generally targeted insulin resistance or oxidative stress. Open-label proof-of-concept studies have utilized changes in serum ALT or liver brightness on ultrasound as endpoints.[190] Agents evaluated thus far include metformin, vitamin E, ursodeoxycholic acid and delayed-release cysteamine.[190] Recently, a large multicenter RCT using change in histology as a secondary endpoint was published.[130] This study, called TONIC, compared the efficacy of vitamin E or metformin to placebo in 8-17 year olds with NAFLD.[130] Although the primary outcome of sustained reduction of ALT was not different among the 3 groups, there were statistically significant improvements in NAS and resolution of NASH ($p<0.006$) with vitamin E treatment compared to placebo over 96 weeks.[130] In this study, metformin administered at 500 mg twice daily dose had no effect on liver biochemistries or liver histology.

Recommendations

43. Intensive lifestyle modification improves aminotransferases and liver histology in children with NAFLD and thus should be the first line of treatment. ***(Strength – 2, Quality – B)***

44. Metformin at 500 mg twice daily offers no benefit to children with NAFLD and thus should not be prescribed. The effect of metformin administered at a higher dose is not known.

(Strength – 1, Quality – B)

45. Vitamin E 800 IU/day (RRR α--tocopherol) offers histological benefits to children with biopsy-proven NASH or borderline NASH but confirmatory studies are needed before it's use can be recommended in clinical practice ***(Strength – 1,Quality – B)***

Table 1. Grading of Recommendations, Assessment, Development and Evaluation (GRADE)

Strength of Recommendation	**Criteria**
Strong [1]	Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost
Weak [2]	Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost or resource consumption
Quality of Evidence	**Criteria**
High [A]	Further research is unlikely to change confidence in the estimate of the clinical effect
Moderate [B]	Further research may change confidence in the estimate of the clinical effect
Low [C]	Further research is very likely to impact confidence on the estimate of clinical effect

Table 2: Common Causes of Secondary Hepatic Steatosis

Macrovesicular steatosis - Excessive alcohol consumption - Hepatitis C (genotype 3) - Wilson's disease - Lipodystrophy - Starvation - Parenteral nutrition - Abetalipoproteinemia - Medications (e.g., amiodarone, methotrexate, tamoxifen, corticosteroids)
Microvesicular steatosis - Reye's syndrome - Medications (valproate, anti-retroviral medicines) - Acute fatty liver of pregnancy - HELLP syndrome - Inborn errors of metabolism (e.g., LCAT deficiency, cholesterol ester storage disease, Wolman disease)

Table 3: Nonalcoholic Fatty Liver Disease and related definitions

Nonalcoholic Fatty Liver Disease (NAFLD)	Encompasses the entire spectrum of fatty liver disease in individuals without significant alcohol consumption, ranging from fatty liver to steatohepatitis and cirrhosis.
Nonalcoholic Fatty Liver (NAFL)	Presence of hepatic steatosis with no evidence of hepatocellular injury in the form of ballooning of the hepatocytes or no evidence of fibrosis. The risk of progression to cirrhosis and liver failure is minimal.
Nonalcoholic steatohepatitis (NASH)	Presence of hepatic steatosis and inflammation with hepatocyte injury (ballooning) with or without fibrosis. This can progress to cirrhosis, liver failure and rarely liver cancer.
NASH Cirrhosis	Presence of cirrhosis with current or previous histological evidence of steatosis or steatohepatitis
Cryptogenic Cirrhosis	Presence of cirrhosis with no obvious etiology. Patients with cryptogenic cirrhosis are heavily enriched with metabolic risk factors such as obesity and metabolic syndrome.
NAFLD Activity Score (NAS)	An unweighted composite of steatosis, inflammation, and ballooning scores. It is a useful tool to measure changes in liver histology in patients with NAFLD in clinical trials.

Table 4: Risk Factors Associated with NAFLD

Conditions with established association	Conditions with emerging association*
Obesity	Polycystic ovary syndrome
Type 2 diabetes mellitus	Hypothyroidism
Dyslipidemia	Obstructive Sleep apnea
Metabolic syndrome**	Hypopituitarism
	Hypogonadism
	Pancreato-duodenal resection

*Few studies suggested that individuals with type1 diabetes have increased prevalence of hepatic steatosis based on liver imaging, but there is limited histological evidence.

** The Adult Treatment Panel III clinical definition of the metabolic syndrome requires the presence of three or more of the following features: (1) waist circumference greater than 102 cm in men or greater than 88 cm in women; (2) triglyceride level 150 mg/dL or greater; (3) high-density lipoprotein (HDL) cholesterol level less than 40 mg/dL in men and less than 50 mg/dL in women; (4) systolic blood pressure 130 mm Hg or greater or diastolic pressure 85 mm Hg or greater; and (5) fasting plasma glucose level 110 mg/dL or greater.[199]

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