REVIEW ARTICLE

NONALCOHOLIC STEATOHEPATITIS: CASE-BASED FOCUSED ON PEDIATRIC AND ADULT GUIDELINES

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KEYWORDS:

NAFLD

Nonalcoholic Fatty Liver Disease

Obesity

Pediatric NASH

Type 2 Diabetes

ABSTRACT:

Nonalcoholic fatty liver disease (NAFLD) comprises a continuum of conditions associated with insulin resistance and obesity in the absence of secondary causes of hepatic steatosis (alcohol, medication, genetic disorders, hepatitis, etc.) The milder, benign form of NAFLD is simple fatty liver or steatosis. Fatty infiltration affects more than 5% of the liver.[1] This is determined by histologic exam, direct quantification or imaging. The range progresses to nonalcoholic steatohepatitis (NASH) and culminates in fibrosis and cirrhosis. Histologic changes include ballooning degeneration of hepatocytes, the presence of Mallory bodies, macrovesicular steatosis, lobular or portal inflammation.[2]

NAFLD is now the foremost cause of childhood, adolescent and adult chronic hepatic disease. The pediatric and adult obesity epidemic makes NAFLD a potentially ubiquitous hepatic pathology amongst all patients.[3,4,5] The increase of obese children and adults with obesity correlates to the rise of NAFLD cases. In adults, the rate of NAFLD increase is paired with the epidemics of obesity and Type 2 Diabetes (T2DM).[4,5] Data proposes hepatic-related mortality may be due to NASH ultimately progressing to cirrhosis.[3,4] NAFLD is linked to pediatric and adult cardiovascular risk and morbidity.[4,6] Non-invasive biomarkers and the gold standard of liver biopsy not only diagnose but assist in targeted therapies.[6] Most pharmacologic therapy for NAFLD is in trial stages for patients of all ages. Pioglitazone is favored in adults who have NAFLD/NASH and T2DM.[7] The gut biome is also impactful. Lifestyle modifications of diet and exercise can reduce the public health burden of this disease.[7,8,9,10]

INTRODUCTION

The prevalence of Nonalcoholic Fatty Liver Disease (NAFLD) among adults and children has increased worldwide.[5] There is a 34% prevalence among children with obesity vs. 7% in the general pediatric population.[2] The classic clinical presentation of NAFLD in the pediatric population typically occurs in patients with obesity or overweight, with a male predominance in the prepubertal age group and a higher occurrence in Hispanic origin. Dyslipidemia can have multiple contributing environmental and genetic influences, such as nutrition, physical inactivity, socioeconomic levels, tobacco exposure, etc. The North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) commissioned a multidisciplinary committee with vested interests to put forth recommendations surrounding screening, diagnosis and pediatric treatment Nonalcoholic Steatohepatitis (NASH). These recommendations will be further discussed in the pediatric case.[11]

The worldwide prevalence of NAFLD and NASH in adults is estimated to be 25% and 3-5%, respectively.[12,13] The clinical presentation of NAFLD in adult patients also parallels metabolic conditions, including diabetes mellitus, dyslipidemia and obesity.[9] Screening patients for NAFLD in this disease setting is not standardized. Other extra-hepatic diseases associated with NAFLD include obstructive sleep apnea, psoriasis, osteoporosis, polycystic ovarian syndrome, primary hypothyroidism, chronic kidney diseases and extra-hepatic cancers.[7] According to Leoni *et al*. in a systematic review of five international guidelines, including the American Association for the Study of Liver Diseases (AASLD), NAFLD screening is approached differently. Only three of the five international guidelines recommend screening "high-risk groups," whereas the AASLD suggested that screening adults with several metabolic risk factors was not cost effective. The European Association for the Study of the Liver (EASL) recommended screening in patients with obesity, metabolic syndrome and abnormal liver enzymes. The National Institute for

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 Print ISSN: 1877-573X
DOI:10.33181/13024

Health and Care Excellence (NICE) and the Asia-Pacific guidelines both recommended screening in patients with obesity and T2DM.

The pathogenesis of NAFLD is poorly defined, yet the persistent "two-hit process" seems to be the most likely hypothesis.[8,14] Lipid accumulation in the liver is most likely due to insulin resistance and hepatic steatosis development. Insulin resistance and ultimate hyperinsulinemia lead to changes to hepatic-free fatty acid uptake, synthesis, degradation and secretion promoting increased triglyceride presence in hepatocytes. This allows the liver to be vulnerable to the second hit—progressive liver damage resulting from the inflammatory response (oxidative stress from dysfunctional mitochondria and proinflammatory cytokines, like TNF-alpha). These contributing factors promote the progression from simple fatty liver to steatohepatitis and ultimately, cirrhosis.[14]

A leading hypothesis proposed a way to limit progressive liver damage by altering the TNF-a pathways.[14] This action will improve insulin sensitivity and reduce steatosis, thereby lowering the free fatty acid levels.[14] One way to augment this process is with the help of protective factors, such as adiponectin. Adipocytes secrete adiponectin at a rate inversely proportional to the BMI level.[8,14] This reinforces the need for lifestyle modifications that lower BMI as a mainstay of treatment.

This article will highlight the approach for pediatric and adult patients with increased risk for NAFLD and co-morbid diseases, including current and future testing and treatment discussions. Among the pediatric and adult patients with risk for NAFLD, many imaging techniques, biomarkers and lifestyle recommendations are similar. Considering the increased mortality with metabolic syndrome and cardiovascular disease in adult patients with NAFLD, medications will be highlighted that are not used in the pediatric population.

CASE 1

A 12-year-old Hispanic male presents for his annual physical exam. He has no significant past medical history. He endorses right upper quadrant pain as well as fatigue. His mother denies snoring or apnea. He endorses a sedentary lifestyle and consumes a diet replete with junk food with little to no fresh fruit or vegetables. His BMI is 30.9, placing the BMI-for-age at the 99th percentile for boys aged 12 years. His blood pressure is 124/82mmHg. He has noted hepatomegaly, acanthosis nigricans on his neck, abdominal striae and obese body habitus on exam. The results of his fasting lipid panel are: total cholesterol 204 mg/dL, LDL-C 140 mg/dL, HDL-C 28 mg/dL and non-HDL-C 150 mg/dL. His triglycerides are 136 mg/dL and albumin is normal at 4 g/dL. His serum alanine aminotransferase is 32 U/L and aspartate aminotransferase are moderately elevated at 30 U/L with a normal AST: ALT ratio of 0.94. Ultrasound of the liver demonstrates a diffuse echogenicity due to the fatty infiltration. His Hgba1c is 5.7%, indicating an increased risk for diabetes, fasting glucose 145 mg/dL causing concern for pre-diabetes: GGT 20 U/L (normal) bilirubin 1.3 mg/dL, additionally, a PHQ-9 is performed that demonstrates a score of moderate depression, without suicidal ideation.

For this 12-year-old male, his epidemiologic risks include his age, gender and ethnic origin. His elevated BMI and blood pressure, as well as hyperinsulinemia, pose further risks.

The NASPGHAN GRADE System (Grading of Recommendations, Assessment, Development and Evaluation) is utilized to stratify both the strength of the recommendations and the evidence quality for screening, diagnosis and treatment. Below are two tables (Tables 1 and 2) of the data extrapolated from both an evidence-based approach and the clinical acumen of the panelists.

TABLE 1:

Screening recommendations based on NASPGHAN Clinical Practice Guidelines for diagnosis and treatment of Nonalcoholic Fatty Liver Disease in children.[11]

STRENGTH OF RECOMMENDATION	QUALITY OF EVIDENCE	RECOMMENDATION
1	B	Ages 9–11 years old for all children with obesity (BMI≥95th percentile) and children who are overweight (BMI≥ 85th and <94th percentile) with risk factors (insulin resistance, central adiposity, pre-diabetes, dyslipidemia, sleep apnea or family history of NAFLD/NASH).
2	B	Earlier screening in younger patients if family history of NAFLD/NASH, severe obesity or hypopituitarism.
2	C.	Screening of siblings and parents of children with NAFLD if known risk factors (obesity, Hispanic ethnicity, insulin resistance, pre-diabetes, diabetes, dyslipidemia).
1	B	The best screening test for NAFLD in children is ALT, but it does have substantial limitations.
1	A	ALT interpretation should be based upon sex-specific upper limits of normal in children (22 U/L for girls and 26 U/L for boys) not individual laboratory upper limits of normal.
1	C	Persistently (>3 months) elevated ALT more than twice the upper limit of normal should be evaluated for NAFLD or other causes of chronic hepatitis.
2	C	ALT >80 U/L warrants increased clinical concern and timely evaluation.
2	C	Follow-up screening for NAFLD is recommended.
2	C	When the initial screening test is normal, consider repeating ALT every two to three years if risk factors remain unchanged.
2	C	Consider repeating screening sooner if clinical risk factors of NAFLD increase in number or severity. Examples include excessive weight gain, T2DM or OSA.

TABLE 2:

Diagnostic recommendations based on NASPGHAN Clinical Practice Guidelines for diagnosis and treatment of Nonalcoholic Fatty Liver Disease in children.[11]

STRENGTH OF RECOMMENDATION	QUALITY OF EVIDENCE	RECOMMENDATION
1	A	Exclude alternative etiologies for elevated ALT and/or hepatic steatosis and investigate the presence of coexisting chronic liver diseases.
1	B	Liver biopsy should be considered for NAFLD assessment in children who have increased risk of NASH and/or advanced fibrosis, such as higher ALT (>80 U/L) splenomegaly, AST/ALT >1, panhypopituitarism, advanced fibrosis and T2DM.
1	B	Ultrasound is not recommended for the determination or quantification of steatosis due to poor sensitivity and specificity. Ultrasound may be useful for assessing other causes of liver disease, such as masses gallbladder disease, changes associated with portal hypertension, etc.
1	B	The use of CT is not recommended for the determination or quantification of steatosis due to radiation risk.

Strength of recommendation (Tables 1 and 2)
Strong [1] Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-reported 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 (Tables 1 and 2)
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 likely to change confidence in the estimate of the clinical effect.

There is an elevation in insulin levels during Sexual Maturity Rating 2, typically around age 8–15 years old with the development of secondary sexual characteristics. This hormonal change may enhance liver fat accumulation. It is unclear if a sedentary lifestyle coupled with poor food choices in the adolescent period can fully explain elevated rates of NASH in this age group.[6] Screening can begin between 9–11 years old for children with obesity (BMI >/= 95 percentile) and children overweight with the following risk factors of insulin resistance, dyslipidemia, sleep apnea, central adiposity or family history of NAFLD/NASH.[2,11] Screening younger patients is usually done on a case-by-case basis if multiple risk factors are present.[2]

Since there is a greater incidence of NAFLD in males vs. females androgens may not only worsen NASH, but estrogens could be a protective factor. Estrogen can lower the progression to atherosclerosis with its anti-inflammatory effects of inhibiting lipid and cholesterol oxidation products. Halting this pathway impedes simple steatosis from developing into NASH. Androgen studies have demonstrated an increase in risk of NAFLD. Males not only have higher insulin resistance levels but also higher levels of triglycerides and lower HDL.[6]

It has been regularly confirmed that there is an ethnic disparity in the number of NAFLD cases, as there are more Mexican Americans than Caucasians affected. There are multifactorial reasons, perhaps due to increased visceral adiposity coupled with insulin resistance at equivalent BMI amongst the groups. These factors may further be influenced by socioeconomic status, diet, activity level and home location/accessibility. It is hard to pinpoint the exact cause that predisposes patients to fatty liver disease. Further studies are needed to elucidate genetic components and possible protective factors.[6]

Histologic differences help stratify the degree of severity of NAFLD. Simple fatty liver does not include hepatocellular injury. NASH and cirrhosis do include hepatocellular injury, both with and without fibrosis. This distinction helps physicians assist in directing treatment plans as weight loss (bariatric) surgery is not routinely indicated in pediatric medicine. Exceptions would include liver biopsy demonstrating advanced fibrosis consistent with NAFLD and the patient also exhibiting comorbidities.[6]

Advanced liver disease with cirrhosis presents with a constellation of physical exam findings: splenomegaly, hardened liver border, spider angiomas, palmar erythema, encephalopathy and jaundice.[11] Screening for NAFLD should be part of the evaluation of pediatric obesity-related conditions, such as T2DM, sleep apnea, early atherosclerotic heart disease and hypertension.[2]

For this patient, recommended lifestyle modifications could include increasing physical activity to 60 minutes every day, diet to include at least five servings of fruits and vegetables and are low in saturated fats, eliminating the consumption of sugar-sweetened beverages, less than two hours a day of screen time, weight loss and referral to a registered dietician. Sustainable weight loss is associated with improved cardiovascular risk and obesity-related comorbidities, such as NAFLD. Weight loss greater than 5% has been shown to have marked improvement in liver histology during adult studies. One pediatric study showed a 5 kg (11.02 lbs.) weight loss demonstrated improvement in NAFLD patient ALT and AST levels.[10] Further studies are needed to determine the most-effective diet (low carbohydrate, low-glycemic index, low-fat diet, etc.)

Treatment goals are to repair the steatosis and inhibit fibrosis (and ultimately cirrhosis) and reduce the overall additional adiposity. Another aim of treatment places emphases on limiting risk factors that worsen NASH prognosis: obesity and T2DM. Treatment should concentrate on averting the two-hit process: limiting fatty liver infiltration (associated with insulin resistance and obesity) and reducing oxidative stress.[14] Patients are encouraged to avoid alcohol, hepatotoxins and certain medications (valproate, acetaminophen, etc.) metabolized in the liver.[14] Binge drinking can further potentiate the development of fibrosis.[11] Baseline labs in addition to possible biopsy, may be done

before initiating hepatotoxic medication. Further anticipatory guidance and counseling include discussing the risk of second-hand smoke exposure and discouraging adolescents against smoking and other nicotine delivery tools. Additionally, patients should be up to date with their vaccinations, especially hepatitis A and B.[11] As briefly alluded to in the clinical vignette, assessing psychosocial issues with appropriate and timely screening is imperative.[11] Addressing any underlying depression is part of the treatment plan as well.[11] This patient had an elevated PHQ-9 score, consistent with depression. Current literature suggests that pediatric patients with obesity lead to lower quality of life and risk of clinical depression.[15] Bullying, poor self-esteem, social stigma, emotional eating and even discrimination are very real emotional ramifications of obesity.[15]

TREATMENT IN CHILDREN

Practice guidelines from the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) state that no currently available medications or supplements for NAFLD have evidence to support their use in children.[11] The AASLD identifies that metformin should not be used in children to specifically treat NASH or NAFLD. Only a few studies of vitamin E in children with biopsy-proven NASH are associated with limited if any benefit.[16,17] However, the AASLD supports consideration of vitamin E in a dose of 800 IU/day for some children with biopsy-proven NASH, weighing risks and benefits since long-term safety is unknown.[17]

A follow-up visit is scheduled for six months to repeat fasting laboratory studies. Despite extensive counseling on diet and exercise by the clinician, the patient has been poorly compliant and has not made any drastic lifestyle changes. His BMI and blood pressure have remained the same. His repeated fasting lipid panel results, including ALT, AST, GGT and alkaline phosphatase, continue to remain elevated. What is the best approach to his risk for NAFLD?

Due to the elevated screening labs, further laboratory evaluation is needed to rule out other causes of liver disease, such as infection/hepatitis, celiac disease, hypothyroidism, genetic and autoimmune liver disease, etc. A liver biopsy can be considered to determine the degree of steatosis, inflammation and whether there is fibrosis present or lobular involvement.

The case for the use of ultrasound in the pediatric population, specifically Transient Elastography, has increased due to not only the growing number of pediatric NASH cases but the need for non-invasive diagnostic modalities to determine levels of liver fibrosis. The innovations of MR Elastography and Shear-Wave US Elastography have greatly improved the sensitivity, but there are still restrictions that make imaging difficult in the pediatric population. These limitations include breathing-induced tissue displacement, biologic tissue differences and variable disease distribution. Time-harmonic Elastography uses a steady, time-harmonic stimulus and helps obese patients because it can detect moderate fibrosis. The innovation of utilizing shear-wave detection will help limit the use of invasive and recurrent procedures, such as frequent liver biopsies. Further studies are needed to investigate the accuracy of ultrasound in pediatric NASH patients to determine stages of fibrosis.[18,19] These recommendations are similar to the adult population, as discussed later in this article.

Further imaging beyond ultrasound can include MRI-PDFF to quantify the degree of steatosis better.[2] The extent of histologic liver damage determines the natural history and prognosis. If simple steatosis, the clinical course is usually benign. However, if NASH is present, cirrhosis and related complications have an increased chance of developing. A liver transplant may be indicated if fibrosis progresses. The disease may even recur after transplantation.

Longitudinal studies are lacking regarding the presence of hepatocellular carcinoma in adults with previous childhood NAFLD. Preventing this potential, dire consequence is the impetus for consistent and diligent screening in at-risk pediatric groups (patients with obesity, insulin resistance or other aspects of metabolic syndrome). Weight loss and lifestyle changes are the mainstays of treatment, while multiple drug trials are pending. Sadly, with the staggering levels of pediatric patients with obesity, pediatric NAFLD and NASH are predicted to only increase. This community burden has dreadful public health consequences if not acted upon appropriately and with a sense of urgency. Perhaps this will shift the public health conversation to promote new policies surrounding school lunch options and activity within the family unit.[8]

CASE 2

A 45-year-old male presents to the family medicine clinic with concern for elevated blood sugars and alcohol use history. Last year, he was seen for a wellness physical and was diagnosed with insulin resistance with an initial Hga1c of 6.0%. During his physical last year, lifestyle changes, including weight loss and exercise, were recommended. One year later, he presents with a weight gain of 20 lbs. He currently smokes ½ pack per day for 15 years, drinks two beers daily and his parents both have T2DM. A physical exam includes BP 148/88 (confirmed on two occasions) and BMI 39 kg/m.2 He is taking no medications. New labs reflect a Hga1c of 7.8% with AST 80 U/L, ALT of 68 U/L, albumin of 4.0 g/dL and platelets of 170 109/L. His total cholesterol is 280 mg/dL, LDL is 160 mg/dL, HDL 35 mg/dL and TG 280 mg/dL. The rest of his metabolic panel is negative. His abdominal exam is consistent with enlarged pannus, non-tender, no masses, no obvious organomegaly.

Approaching this patient's health risks is multifactorial. He has new-onset T2DM, elevated blood pressure, liver enzymes and cholesterol. Cumulatively, this is metabolic syndrome.[20] (Table 3)

TABLE 3:

Criteria required for metabolic syndrome[20]

CRITERIA (THREE OF FIVE REQUIRED)	INCLUSION RANGE
Waist measurement	35 inches or more for women or 40 inches or more for men
Triglyceride level	150 mg/dL or higher
HDL cholesterol level	Less than 50 mg/dL for women; less than 40 mg/dL for men
Blood pressure	130/85 mmHg or higher
Fasting blood sugar	100 mg/dL or higher

The patient presents with significant cardiovascular disease risk and possible NAFLD or even NASH. Further work-up is recommended and risk factor reduction is critical. It is important to consider that the pathogenesis of obesity, T2DM, NAFLD and CVD share many disease pathways. Evidence has also supported findings of increased chronic kidney disease in patients with NAFLD.[13] It is well documented that NAFLD and NASH with cardiovascular disease increases overall mortality.[13] Evidence also supports that metabolic syndrome promotes a faster progression of NASH to cirrhosis, leading to a liver transplant.[13] Given this liver enzyme elevation and working diagnosis of NAFLD or possibly NASH, a comprehensive cardiac exam should be completed. Using the American College of Cardiology Atherosclerotic Cardiovascular Disease (ASCVD) Risk Estimator[21] that includes the patient's age, tobacco use, a new diagnosis of T2DM and lipid values, his 10–year risk is high at 32.2%. Recommendations to reduce this risk include blood pressure control (Table 4), weight loss (Table 5), lipid-lowering agents, blood sugar control and smoking cessation.[21] The benefit of using statins in patients with NAFLD or NASH to reduce cardiac risk may outweigh the risk of the potential increases in liver enzyme levels. Blood sugar control for patients with NAFLD/ NASH currently includes pioglitazone. See Table 6 for medication discussions.

TABLE 4:

Blood pressure control recommendations, American Diabetes Association (ADA)[22]

GRADE	RECOMMENDATION
C	For individuals with diabetes and hypertension at higher cardiovascular risk (existing atherosclerotic cardiovascular disease or 10–year atherosclerotic cardiovascular disease risk >15%), a blood pressure target of <130/80 mmHg may be appropriate if it can be safely attained.
A	Patients with confirmed office-based blood pressure ≥140/90 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of pharmacologic therapy to achieve blood pressure goals.
A	Treatment for hypertension should include drug classes demonstrated to reduce cardiovascular events in patients with diabetes (ACE inhibitors, angiotensin receptor blockers, thiazide-like diuretics or dihydropyridine calcium channel blockers).

A—Clear evidence from well-conducted, generalizable randomized controlled trials that are adequately powered • B—Supportive evidence from well-conducted cohort studies • C—Supportive evidence from poorly controlled or uncontrolled studies • E—Expert consensus or clinical experience

Some patients with normal liver enzymes have been diagnosed with NAFLD.[7] Given this patient's elevated AST, ALT and diagnosis of metabolic syndrome; he is at increased risk for NASH and fibrosis. According to the American Diabetes Association, grade C recommendation, determining the extent of his liver disease is the next step. Non-invasive testing measures for this patient are considered first, which include both imaging and biomarkers. Many of these non-invasive tests can be ordered by the primary care physician. These non-invasive methods have increased accuracy and can be used to rule out advanced disease. Consulting with a hepatologist and endocrinologist may help with test interpretation and disease staging.[4]

According to a systematic review by Leoni *et al*. of five international guidelines, including the American Association for the Study of Liver Diseases (AASLD), imaging recommendations include a consensus for using abdominal ultrasound as a first-line approach. Ultrasound can identify steatosis as mild, moderate and severe. Pooled sensitivities and specificities to distinguish moderate to severe fatty liver from the absence of steatosis has been reported for ultrasound at 85% (80–89%) and 93% (87%–97%), respectively.[12] However, the accuracy of ultrasound to diagnose steatosis in patients with a BMI > 40 is reduced.[7] Transient Elastography (TE) is the technique of choice that uses both ultrasound and low-frequency elastic waves to quantify liver fibrosis (88–89% accuracy). TE produces a liver stiffness measurement (LSM). Imaging can also be performed with magnetic resonance elastography (MRE), however, this increases the cost and is most often used in clinical trials. Several studies are underway in efforts to replace liver biopsy with this non-invasive imaging measurements.[12]

Non-invasive biomarkers can be used for fibrosis prediction and risk stratification. The most suggestive markers in this patient include the elevated AST and ALT. Other common markers in NAFLD include elevated serum ferritin and low titers of autoimmune disease antibodies.[7] Several of these biomarkers have been incorporated into predictive models; however, many have not been validated.[12] Two fibrosis scoring methods that have been clinically validated include the FIB-4 and NAFLD Fibrosis Score (NFS), which also predict cardiovascular risk with high sensitivity and specificity. Overall, for these two scoring methods, reported positive predictive values of 80% and negative predictive values of 90% had been confirmed.[4,7,12] The FIB-4 score uses age, AST, ALT and platelets and the NFS uses age, BMI, IFG and diabetes, AST to ALT ratio, platelets and albumin. A FIB-4 score of < 1.3 or an NFS score of < -1.455 would suggest a low risk of advanced fibrosis. This patient's FIB-4 score is 2.57 and NFS score of 1.10 (correlates to F3-F4 fibrosis level). His higher FIB-4 or NFS scores predict intermediate-risk or higher and TE imaging is recommended. An intermediate or high risk of fibrosis determined by TE is considered an LSM of ≥ 8KPa and a liver biopsy should be considered for confirmation.[12] Studies that combine the FIB-4 or NFS with TE have reported increased diagnostic accuracy.[7,12] Several guidelines agree that liver biopsy should be performed if the diagnosis is uncertain or when NAFLD- related advanced (intermediate-high risk) disease is suspected by scoring or imaging.[23] If the scores are low, testing should be repeated every two years.[7] Patients with NASH or fibrosis should be screened annually. Although the

AASLD does not provide an algorithm for diagnosis or follow up strategies for advanced fibrosis, they do support the strength of evidence of these non-invasive testing methods that are regularly used by the other guidelines.[7]

TABLE 5:

Nutritional recommendations for both NAFLD, NASH and T2DM are similar.[7,9]

Reduction in caloric intake	A diet of 1200-1600 kcal/d, low fat (less than 10% saturated fat) and low carbohydrate (< 50% of total kcal) foods. The Mediterranean diet (plant-based, high in antioxidants and anti-inflammatory) is most commonly discussed among experts. Avoiding crash diets, limiting excess alcohol consumption (<40 g/d) and at least 7-10% weight loss is recommended.
Exercise	Aerobic and resistance training > 150 minutes per week.
Supplements	Vitamin E at 800 IU/d has been shown to decrease liver enzymes and histological inflammation improvement.; however, long term safety data shows conflicting evidence. See Table 6 for further discussion.
Bariatric surgery	Patients who are unresponsive to lifestyle changes and pharmacotherapy. Surgery has been shown to improve steatosis but is not unanimously recommended among all five of the systematic review guidelines.

The AASLD suggests that management of NAFLD focus on the common comorbidities of obesity, hyperlipidemia and T2DM. There are no FDA-approved medications specific to NAFLD currently marketed in the U.S. The AASLD recommends limiting drug therapy focused on the liver disease to only those with biopsy-proven NASH and fibrosis.[17]

INSULIN SENSITIZERS

Insulin resistance is a common finding in patients with NASH. Pioglitazone is a PPAR-γ receptor agonist and is the most-studied thiazolidinedione for NAFLD. Studies of pioglitazone 30 mg per day demonstrated improved aminotransferases as well as histologic findings of NASH. The most common adverse event associated with pioglitazone is weight gain, ranging from approximately 2.5 to 5 kg in clinical trials. Pioglitazone is associated with decreased bone density with long term use. Data are conflicting with regard to an increased risk of bladder cancer. Overall, the AASLD supports the use of pioglitazone in adults with biopsy-proven NASH with or without T2DM.[17] Other antidiabetic agents have been evaluated for NASH. GLP-1 receptor agonists, such as liraglutide, show promise in initial trials evaluating the resolution of NASH.[24] The most recent guidance from AASLD suggests it is too early to consider treating liver disease with these agents. Metformin, however, has not been shown to be beneficial for NASH and is not recommended for this use by the AASLD.[17]

VITAMIN E

The antioxidant properties of vitamin E have generated interest in its use for NASH. The clinical trials of vitamin E typically included patients without diabetes and vary widely in the formulation and dosing of vitamin E, duration of treatment and concomitant lifestyle changes. General findings of the studies associate it with decreased aminotransferases and improvement in steatosis and inflammation.[16,17] The AASLD recommends considering a dose of 800 IU per day for adults with biopsy-proven NASH who do not have diabetes.[17] Importantly, the AASLD recommends against the use of vitamin E in patients with NAFLD without liver biopsy, NASH cirrhosis or cryptogenic cirrhosis, as it has not been adequately studied in these populations. It is also recommended to weigh the potential for increased bleeding risk and prostate cancer in individualized treatment decisions.[16,17]

OTHER THERAPIES

Lipid-lowering therapy is an important modifier of cardiovascular risk in patients with NAFLD. While statin medications such as atorvastatin have demonstrated variable results in improving aminotransferases in this population, they continue to be an important option for treating hyperlipidemia in patients with NAFLD or NASH. The AASLD suggests avoiding treatment in those with decompensated cirrhosis.[17]

Studies of omega-3 fatty acids do not show consistent benefit for liver disease associated with NAFLD or NASH. However, the AASLD suggests continued use of omega-3 fatty acids for treatment of hypertriglyceridemia in patients with NAFLD.[17]

Although ursodeoxycholic acid (ursodiol) has been studied to improve hepatic parameters in NAFLD and NASH, data are conflicting and represent small trials with a varied endpoint. The AASLD recommends against its use.[17]

EMERGING THERAPIES

There is a great need for expanded pharmacotherapy options for NASH. Drug molecules that target modulators of hepatic inflammation, fibrosis, energy metabolism, fatty acid synthesis and the gut microbiome are under investigation and in various development phases.[25] Obeticholic acid and elafibranor are examples of agents further in the pipeline. Obeticholic acid is a farnesoid X receptor agonist currently under investigation for use in NAFLD. It is FDA-approved for primary biliary cholangitis who have an inadequate response to ursodiol. Younossi and colleagues[26] recently published findings from an interim analysis of a dose ranging placebo-controlled study of obeticholic acid in over 900 adults with NASH (stage F2–F3 fibrosis). The 25 mg daily dose showed significant improvement in fibrosis and the study is ongoing. Adverse events included pruritis and elevations in LDL cholesterol. The AASLD does not recommend off-label use of this agent currently, pending findings and analysis of the clinical outcomes once the trial is complete.[17] Multiple insulin sensitizing agents are under clinical investigation for NASH and fibrosis. A placebo-controlled dose-ranging study of elafibranor, a dual PPAR

α-δ receptor agonist, demonstrated a trend towards improved NASH without fibrosis worsening.[27] Further trials are ongoing to determine its potential place in therapy.

TABLE 6:

Medication recommendations for adults with NASH[a]

DRUG THERAPY[b]	CONSIDERATIONS
Pioglitazone	Consider use in biopsy-proven NASH in patients with or without diabetes
Metformin	Not recommended for this indication
GLP-1 agonists	Currently under investigation; insufficient evidence for clear guidance at this time
Vitamin E	Consider use in biopsy-proven NASH in patients without diabetes
Ursodeoxycholic acid	Not recommended
Statins	Supported for treatment of hyperlipidemia in patients with NAFLD/NASH unless decompensated cirrhosis/acute liver failure
Omega-3 Fatty Acids	Supported for treatment of hypertriglyceridemia in patients with NAFLD

[a] Recommendations from the American Association for the Study of Liver Diseases[17]
[b] No drug therapies are currently approved for this indication by the U.S. Food and Drug Administration

GUT MICROBIOME

There is an emerging pool of studies evaluating gut microbiota and liver disease. Metabolic diseases have been linked to diet induced imbalance of the gut, also known as "leaky gut."[28] Increased intestinal permeability or leaky gut is common in patients with NAFLD, which allows a larger amount of bacteria-derived products to enter the portal circulation.[29] This enhances the amount of damage incurred by the liver, which hastens the conversion from healthy tissue to the fibrotic tissue seen in NASH.[29] This has led to the development of what many are calling the gut-liver axis, which recognizes the direct connection the liver has to the gut via the portal system.[28] The microbiota of the gut changes in composition with diet; therefore, the liver is exposed to different compounds produced by the microbiota based on their presence or absence in the gut.[29] As a result, one potential solution for combating metabolic diseases, such as NASH, caused by the disruption of the gut-liver axis includes synbiotic supplementation.[23]

Synbiotic supplementation includes the categories of probiotics and prebiotics.[23] Probiotics are microorganisms that confer beneficial effects on the host, while prebiotics are non-digestible carbohydrates that act as a nutrient source for favorable microorganisms in the colon.[23] One study by Ferolla *et al*. has shown promising results in using synbiotic supplements to modulate the gut flora. In this study comprised of 50 test subjects 27 with NASH and 23 without NASH, it was found that synbiotic supplementation with lifestyle changes is superior to lifestyle changes alone on the variables of BMI, waist circumference and body weight.[23] Steatosis, on the other hand, only showed attenuation with synbiotic supplementation.[23] The small sample size and differences in the experimental and control groups likely interfered with how robust this study's results were.[23] Given this information, the study by Ferolla *et al*. still showed promising results that should be explored further.

Synbiotic supplementation could be beneficial for NASH patients, given its effects on BMI, waist circumference and body weight, in that lowering these parameters could slow disease progression.[23] Also, synbiotic supplementation may be a solution that brings back the beneficial gut bacteria, allowing reestablishment of the gut-liver axis. There may still be a "leaky gut" due to previously damaged liver tissue, but the gut microbiota would no longer contribute to that damage, which may allow the liver the time it needs to heal itself. The question that remains is, which sets of bacteria would provide the best results? With further experimentation and more robust studies, symbiotic supplementation could prove to be an easily accessible solution for NASH patients.

CONCLUSION

One of the goals of this article was to highlight the epidemic of obesity in both the adult and pediatric populations and nonalcoholic steatohepatitis and the complications of the disease. The research brings consideration to a topic that does not receive a lot of attention in primary care and can help direct the approach to screening and treatment. As there is no clear consensus, even amongst academic societies, clinicians can use the data to determine their patients' course of action. This article seeks to provide information to modify current practices by utilizing emerging data. Primary care physicians should be cognizant of the signs of nonalcoholic steatohepatitis, incorporate cost-effective and judicious screening tests and encourage lifestyle modifications. The emerging literature surrounding the gut microbiome and medications encourages further research. Longitudinal studies are lacking but would provide helpful information regarding future implications of the disease process.

TABLE 7:

Abbreviations

AASLD	American Association for the Study of Liver Diseases
ADA	American Diabetes Association
ALT	Alanine Aminotransferase
ASCVD	Atherosclerotic Cardiovascular Disease
AST	Aspartate Aminotransferase
BMI	Body Mass Index
BP	Blood Pressure
CT	Computerized Tomography
FDA	U.S. Food and Drug Administration
FIB-4	Fibrosis 4 Score
GGT	Gamma Glutamyl Transferase
GGTP	Gamma Glutamyl Transpeptidase
HDL	High-Density Lipoprotein
HDL-C	High-Density Lipoprotein-Cholesterol
HgbA1c	Hemoglobin A1c
IU	International Units
LDL	Low-Density Lipoprotein
LDL-C	Low-Density Lipoprotein-Cholesterol
LSM	Liver Stiffness Measurement
MRE	Magnetic Resonance Elastography
MRI-PDFF	Magnetic Resonance Imaging Proton Density Fat Fraction
NAFLD	Nonalcoholic Fatty Liver Disease
NASH	Nonalcoholic Steatohepatitis
NASPGHAN	North American Society of Pediatric Gastroenterology, Hepatology and Nutrition
NFS	NAFLD Fibrosis Score
Non-HDL-C	Non-High Density Lipoprotein Cholesterol
PHQ-9	Patient Health Questionnaire 9
T2DM	Type 2 Diabetes Mellitus
TE	Transient Elastography
TG	Triglycerides

AUTHOR DISCLOSURES: No relevant financial affiliations or conflicts of interest. If the authors used any personal details or images of patients or research subjects, written permission or consent from the patient has been obtained. This work was not supported by any outside funding.

REFERENCES:

1. Abd El-Kader, S. M., & El-Den Ashmawy, E. M. (2015). Nonalcoholic fatty liver disease: The diagnosis and management. *World Journal of Hepatology*, 7(6), 846– 858. https://doi.org/10.4254/wjh.v7.i6.846
2. Mouzaki, M. &Xanthakos, S. (2019). Nonalcoholic fatty liver disease in children and adolescents. Retrieved from https://www.uptodate.com/contents/nonalcoholic-fattyliver-disease-in-children-and-adolescents.
3. Patton HM, Sirlin C, Behling C, et al. Pediatric nonalcoholic fatty liver disease: a critical appraisal of current data and implications for future research. *Journal of Pediatric Gastroenterology and Nutrition*. 2006 Oct;43(4):413-427. DOI: 10.1097/01.mpg.0000239995.58388.56
4. Stefan N, Haring HU, Cosi K. Non- alcoholic fatty liver disease: causes, diagnosis, cardiometabolic consequences, and treatment strategies. *The Lancet Diabetes and Endocrinology*. 2019;7(4), 313-324. doi: https://doi.org/10.1016/S2213-8587(18)30154-2
5. Younossi ZM, Nonalcoholic fatty liver disease- a global health perspective. *J Hepatol Mar* 2019;70:531-44 doi: 10.1016/j.jhep.2018.10.033
6. Loomba, R. , Sirlin, C.B., Schwimmer, J.B., &Lavine, J.E. (2009). Advances in Pediatric Nonalcoholic Fatty Liver Disease. *Hepatology*, Vol. 50, No. 4, 1282- 1291. doi.org/10.1002/hep.23119
7. Leoni S, Tovoli F, Napoli L, Serio I, Ferri S, Bolondi L. Current guidelines for the management of nonalcoholic fatty liver disease: A systematic review with comparative analysis. *World J Gastroenterol*. 2018;24(30):3361–3373. doi:10.3748/wjg.v24.i30.3361
8. Berardis, S., Sokal, E. Pediatric nonalcoholic fatty liver disease: an increasing public health issue. *Eur J Pediatr* 173, 131–139 (2014). http://doi.org/10.1016/j.jpeds.2009.06.014
9. George ES, Forsyth A, Itsiopoulos C, et al. Practical Dietary Recommendations for the Prevention and Management of Nonalcoholic Fatty Liver Disease in Adults. *Adv Nutr*. 2018;9(1):30–40. doi:10.1093/advances/nmx007
10. Zelber-Sagi, S., Godos, J., & Salomone, F. (2016). Lifestyle changes for the treatment of nonalcoholic fatty liver disease: a review of observational studies and intervention trials. *Therapeutic Advances in Gastroenterology*, 9(3), 392– 407. https://doi.org/10.1177/1756283X16638830
11. Vos MB, Abrams SH, Barlow SE, et al. NASPGHAN clinical practice guidelines for the diagnosis and treatment of Nonalcoholic Fatty Liver Disease in children: recommendations from the Expert Committee on NAFLD (ECON) and the North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN). *Journal of Pediatric Gastroenterology and Nutrition*. 2017;64(2):319-34.
12. Castera L, Friedrich-Rust M, Loomba R. Noninvasive Assessment of Liver Disease in Patients with Nonalcoholic Fatty Liver Disease. *Gastroenterology*. 2019 Apr;156(5):1264- 1281.e4. doi: 10.1053/j.gastro.2018.12.036
13. Mantovani A, Scorletti E, Mosca A, et al. Complications, morbidity and mortality of nonalcoholic fatty liver disease. *Metabolism - Clinical and Experimental*, 2020. https://doi.org/10.1016/j.metabol.2020.154170
14. Wieckowska, Anna & Feldstein, Ariel. (2005). Nonalcoholic fatty liver disease in the pediatric population: A review. *Current Opinion in Pediatrics*. 17. 636-41. 10.1097/01.mop.0000172816.79637.c5
15. Schwimmer JB, Burwinkle TM, Varni JW. Health-Related Quality of Life of Severely Obese Children and Adolescents. *JAMA*. 2003;289(14):1813–1819. doi:10.1001/jama.289.14.1813

16. Amanullah I, Habib Khan Y, Anwar I, et al. Effect of vitamin E in nonalcoholic fatty liver disease: a systematic review and meta-analysis of randomized controlled trials. *Postgrad Med*. 2019;95:601-611.

17. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of Nonalcoholic Fatty Liver Disease: practice guideline from the American Association for the Study of Liver Diseases. *Hepatology*. 2018;67(1):328-357.

18. Hudert CA, Tzschatzsch H, Guo J, *et al.* Hudert CA, Tzschatzsch H, Guo J, et al. US Time-Harmonic Elastography: Detection of Liver Fibrosis in Adolescents with Extreme Obesity with Nonalcoholic Fatty Liver Disease. *Radiology.* 2018: 288:1, 99-106.

19. Xanthakos, Stavra A. et al. Use of Magnetic Resonance Elastography to Assess Hepatic Fibrosis in Children with Chronic Liver Disease. *The Journal of Pediatrics*. 2014. Volume 164, Issue 1, 186 – 188.

20. U.S. Department of Health and Human Services "*Metabolic Syndrome.*" *National Heart Lung and Blood Institute,* Jan. 2019, htttp://www.nhlbi.nih.gov/health-topics/metabolic-syndrome.

21. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [published correction appears in Circulation. 2019 Jun 18;139(25):e1182-e1186]. *Circulation.* 2019;139(25):e1082-e1143. doi:10.1161/CIR.0000000000000625 accessed 5/31/2020.

22. American Diabetes Association. Comprehensive Medical Evaluation and Assessment of Comorbidities: Standards of Medical Care in Diabetes—2020. *Diabetes Care* Jan 2020, 43 (Supplement 1) S37-S47; DOI: 10.2337/dc20-S004

23. Ferolla SM, Couto CA, Costa-Silva L, et al. Beneficial Effect of Synbiotic Supplementation on Hepatic Steatosis and Anthropometric Parameters, But Not on Gut Permeability in a Population with nonalcoholic steatohepatitis. *Nutrients*. 2016;8(7)

24. Armstrong MJ, Gaunt P, Aithal GP, et al. Liraglutide safety and efficacy in patients with nonalcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomized, placebo controlled phase 2 study. *Lancet*. 2016;387:679-90

25. Neuschwander-Tetri BA. Pharmacologic management of nonalcoholic steatohepatitis. *Gastroenterology and Hepatology*. 2018;14(10):582-9.

26. Younossi AM, Loomba R, Rinello M, et al. Obeticholic acid for the treatment of nonalcoholic steatohepatitis: interim analysis from a multicentre, randomized, placebocontrolled phase 3 trial. *Lancet* 2019;394:2184-96.

27. Ratziu V, Harrison SA, Francque S, et al. Elafibranor, an agonist of the peroxisome Profliferator-Activated Receptor-α and –δ, induces resolution of nonalcoholic steatohepatitis without fibrosis worsening. *Gastroenterology*. 2016;150:1147-59.

28. Usami M, Miyoshi M, Yamashita H. Gut microbiota and host metabolism in liver cirrhosis. *World J Gastroenterol*. 2015;21(41):11597-11608.

29. Biolato M, Manca F, Marrone G, et al. Intestinal permeability after Mediterranean diet and low-fat diet in nonalcoholic fatty liver disease. *World J Gastroenterol*. 2019;25(4):509-520.