Nonalcoholic Fatty Liver Disease in Children

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Abstract: Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease worldwide. It represents a spectrum of disease from simple hepatic steatosis to steatohepatitis that may develop into progressive hepatic fibrosis and even cirrhosis. NAFLD is the most rapidly increasing indication for liver transplantation in adults. In children, the incidence of NAFLD has also increased over the past decade. Although the majority of children with NAFLD are overweight or obese, there is an increasing subset of children with normal body mass index with so-called lean NAFLD. NAFLD in children is associated with several extrahepatic manifestations, including hyperlipidemia, insulin resistance, and obstructive sleep apnea. The pathogenesis of NAFLD in children involves a multifactorial interaction among genetics, in utero exposures, early childhood exposures, and ongoing nutritional exposures. Although there are some similarities between pediatric NAFLD and adult NAFLD, liver biopsies in children show histologic differences between the two. The current standard-of-care treatment of NAFLD in children is lifestyle change to decrease caloric intake and increase physical activity. There are no medications currently approved for the treatment of NAFLD in children. This article aims to summarize the current understanding of pediatric NAFLD and future directions for intervention and therapeutic aims.

Keywords
Nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, obesity, children, chronic liver disease

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of hepatitis in adults and children.[1] NAFLD encompasses a spectrum of disease, from simple hepatic steatosis to nonalcoholic steatohepatitis (NASH). NAFLD is a chronic liver disease that is more likely to progress to cirrhosis when NASH is present. NAFLD is an increasingly common indication for liver transplantation among adult patients and is the leading indication for liver transplantation among adult women.[2] This article aims to summarize the current understanding of pediatric NAFLD and future directions for intervention and therapeutic aims.

Table. Pediatric Screening Guidelines

Population Specifics	Age	Tests	Action
Children with obese BMI (BMI ≥95th percentile)	9-11 years[a]	ALT Routine ultrasound not recommended as screening test for NAFLD	1. Use age- and sex-specific ULN (22 U/L for girls and 26 U/L for boys) 2. Elevated ALT (≥2 × ULN) for >3 months should be evaluated for NAFLD and other causes of chronic hepatitis 3. ALT >80 U/L should lead to expedited evaluation 4. If ALT is normal, repeat screening every 2-3 years if risk factors remain the same, and sooner if new risk factors develop
Children with overweight BMI (BMI ≥85th percentile and ≤94th percentile) with the following risk factors: • Central adiposity • Insulin resistance • Prediabetes/diabetes • Dyslipidemia • Sleep apnea • Family history of NAFLD/NASH	9-11 years		
Siblings and parents of children with NAFLD with risk factors for NAFLD	N/A		

ALT, alanine aminotransferase; BMI, body mass index; N/A, not applicable; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; ULN, upper limit of normal.

[a]Earlier screening can be considered if severe obesity, family history of NAFLD/NASH, or hypopituitarism is present.

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Epidemiology

NAFLD is estimated to affect 25% of the worldwide population, and roughly 80 million people, both children and adults, have NAFLD in the United States.[3] The prevalence of NAFLD in the pediatric population is estimated to be 13% (9.8% adjusted) with an age-dependent increase in prevalence from less than 1% among children aged 2 to 4 years to 17% in adolescents.[4] In a more recent study of 582 children (50% Black) in New York City who died 48 hours after presentation to medical care, the prevalence of NAFLD was found to be lower, at around 4.5%.[5] Furthermore, the incidence of NAFLD in children has dramatically increased from 36/100,000 in 2009 to 58.2/100,000 in 2018 in parallel with the worsening pediatric obesity epidemic.[6] With the low rate of adherence to NAFLD screening guidelines, however, the true prevalence and incidence of NAFLD among children are likely underappreciated.[6,7] In a study using histologic assessment of children with chronic hepatitis, more than one-third of obese children had NAFLD.[4] Race and sex are also well-described risk factors for NAFLD. Male children have a higher risk of NAFLD than female children, with reported male predominance of obese adolescent NAFLD patients.[8,9] Approximately one-third of obese male children and one-quarter of obese female children are estimated to have NAFLD.[10] Asian-American and Hispanic children are also thought to be at higher risk of NAFLD.[11,12] African-American race appears to be protective against NAFLD, even among obese African-American children.[13]

Clinical Presentation

NAFLD in children and adults represents a spectrum of disease ranging from hepatic steatosis to chronic hepatitis that progresses to end-stage liver disease.[14] Although hepatic steatosis is a bland condition, it is referred to as NASH when it is associated with inflammation and cell injury. Although NASH can regress with intervention, NASH can also progress to cirrhosis, even in children.[15] NASH is associated with an increased risk of hepatocellular carcinoma, even without cirrhosis, although this has been reported rarely in children.[16,17]

Children with NAFLD are nearly always asymptomatic at diagnosis. When symptoms are present, right upper quadrant pain has been thought to be a possible result of the hepatic capsule stretching from hepatic fat deposition, leading to hepatomegaly and/or elevated alanine aminotransferase (ALT).[4] However, in these cases, NAFLD may be an incidental finding. In 2007, the American Academy of Pediatrics published expert consensus recommendations for screening for NAFLD with ALT testing in overweight children with other risk factors or obese children starting at the age of 10 years.[18] When an overweight or obese patient has an ALT greater than or equal to 2 times the upper limit of normal (ULN), evaluation for other causes of liver disease is recommended before a diagnosis

of NAFLD can be made (Table).[19] The ULN for ALT in male children is 26 U/L and in female children is 22 U/L.[19] However, in a recent multicenter, retrospective study of 900 overweight or obese children in the United States referred for evaluation of NAFLD, only 2% were diagnosed with an alternative cause of liver disease, and no children were diagnosed with Wilson disease or autoimmune hepatitis.[20] This study supports the findings of previous research showing that further investigation of elevated ALT in overweight children may be low yield.[21]

NAFLD is considered by some to be the hepatic manifestation of the metabolic syndrome, although it is not included in the current definition of the metabolic syndrome.[22] In adults, cardiovascular disease is the leading cause of death in patients with NAFLD.[23] Children with NAFLD have higher rates of dyslipidemia, hypertriglyceridemia, hypertension, diabetes, and cardiac ventricular dysfunction. Children may present with acanthosis nigricans as a manifestation of insulin resistance.[13] Overall, children with obesity are at increased risk of poor quality of life, and patients with NAFLD specifically have lower physical and mental health scores on standardized assessment.[24] A recent prospective study of 160 adolescents with biopsy-proven NAFLD demonstrated a higher-than-expected incidence of anxiety (odds ratio [OR], 1.09) and depression (OR, 1.60) compared with the general population, suggesting that mental health disorders may also be associated with NAFLD in children.[25]

Lean Nonalcoholic Fatty Liver Disease

NAFLD diagnosed in nonobese or overweight individuals is referred to as lean NAFLD or nonobese NAFLD. These nonobese patients may have increased abdominal adiposity or visceral adiposity despite a body mass index (BMI) in the normal range.[26] This entity has been better described in adults. In children, the mean weighted prevalence of lean NAFLD is estimated to be 8% based on a retrospective study from the National Health and Examination Survey from 2005 to 2014 of 1482 children with a BMI of less than the 85th percentile with elevated ALT levels.[27] Despite a normal BMI, patients with lean NAFLD tend to have higher blood pressure, fasting blood sugar, and rates of dyslipidemia compared with healthy controls.[28,29] Detection of lean NAFLD can be challenging, given the current screening guidelines based on BMI and the asymptomatic nature of NAFLD. There are currently no published studies on the natural history or prognosis of lean NAFLD in children.

Pathogenesis

The pathogenesis of NAFLD is thought to be similar in adults and in children. NASH is characterized by hepatocyte injury and cell death on liver histology.[30] Excess hepatic lipid deposition alone is unlikely to be the sole driver of hepatic inflammation and injury, given that population studies show that hepatic steatosis is 3 times more common than NASH.[3] Increased triglyceride deposition drives progressive liver inflammation by promoting immune activation leading to hepatic injury in a proinflammatory host.[31] This further increases the susceptibility to other stressors without truly protecting against hepatocyte cell death.[32] Ballooned hepatocytes in NASH may trigger regenerative and profibrotic processes mediated by cell types not seen frequently in healthy livers.[33] These processes lead to hepatic fibrosis and cirrhosis in the setting of ongoing liver injury owing to NASH.[34]

A multiple-hit hypothesis of NAFLD postulates that a cascade of factors acts in genetically predisposed individuals and leads to the spectrum of disease.[35] Multiple environmental factors have been the subject of intensive research and, in the case of pediatric NAFLD, have focused on perinatal and early childhood environmental exposures, specific nutritional exposures, and sleep disturbances.

Genetics

A large body of evidence supports that NAFLD is heavily influenced by heritable factors. This is supported by the epidemiologic evidence of large interethnic variation in the risk of NAFLD, as already reviewed. Multiple studies show that the risks of both hepatic steatosis and hepatic fibrosis are increased among family members with NAFLD, including a nearly 12 times higher risk of fibrosis among patients who have first-degree relatives with NASH cirrhosis.[36-38] Romeo and colleagues identified that gene variation in *PNPLA3* contributes to differences in hepatic fat content and NAFLD across different ethnic groups, with the highest frequency of the *PNPLA3-148M* allele in Hispanics (0.49), followed by Americans of European descent (0.23), and finally African Americans (0.17).[39] The *PNPLA3-148M* allele was associated with higher ALT and aspartate aminotransferase (AST) levels among Hispanics in that same study, which shows its association with hepatic inflammation. The *rs738409[G]* allele of *PNPLA3* was most commonly found among Hispanics, with a 2-fold increase in hepatic fat among homozygous individuals than in noncarriers. The *PNPLA3-148M* allele has also been found to impact hepatic fibrosis and liver disease progression in NAFLD and other liver diseases.[40] In the past 10 years, several other polymorphisms have been identified that may modify the development and progression of NAFLD. Specifically, the *rs58542926 C>T* single nucleotide polymorphism, which leads to the *E167K* variant in transmembrane 6 superfamily member 2 (*TM6SF2*), has been

shown in studies to increase susceptibility to liver damage and increase hepatic fat accumulation by decreasing very low-density lipoprotein–mediated lipid secretion. In 1 cohort of patients with biopsy-proven NAFLD, carriers of the *TM6SF2 E167K* variant were more likely to have severe steatosis and fibrosis (P<.05) and more likely to have NASH (OR, 1.84) and advanced fibrosis (OR, 2.08).[41] Other gene variants include glucokinase regulator (*GCKR*) and membrane-bound O-acyltransferase 7 (*MBOAT7*).[42] An emerging field of nutritional genomics studies whether the interaction of these genetic variants with specific nutritional interventions in patients with NAFLD can improve liver health.[43] A recent study examined the impact of specific micronutrient intake and *PNPLA3* variants among a cohort of non-Hispanic males with biopsy-proven NAFLD and showed that the *PNPLA3* variant significantly modifies the relationship between several specific micronutrients and the severity of hepatic fibrosis.[44]

There is increasing evidence that specific perinatal exposures during early childhood confer increased risk for NAFLD. A multicenter, cross-sectional study of 538 children with biopsy-proven NAFLD from the Nonalcoholic Steatohepatitis Clinical Research Network (NASH-CRN) Database has shown that children with both high and low birth weight had higher odds of NAFLD than children with average birth weight.[45] Children with high birth weight had higher odds (OR, 1.82) of having severe steatosis and NASH (OR, 2.03) compared with children with average birth weight. Additionally, the children included in this study with a low birth weight also had higher odds of advanced fibrosis (OR, 2.23). Children born to mothers who had hyperglycemia or experienced rapid weight gain during pregnancy are at higher risk of NAFLD.[46] Neonates born to obese mothers have an increased intrahepatocellular lipid accumulation, which correlated with maternal BMI.[47,48] Furthermore, a mouse model has been developed that shows that infant dysbiosis in pups born to obese mothers may explain increased inflammation and higher risks of NAFLD seen in this population.[49]

Early childhood nutritional exposures may also play a role in the development of NAFLD in children. Early high exposure to sugar, and specifically fructose, including in utero, has been shown to be obesogenic.[50-53] A large cohort study from Australia prospectively collected data on maternal pregnancy and feeding practices and then assessed 1170 children at age 17 years for NAFLD using ultrasonography. The study found that adolescents who were breastfed for at least 6 months and who were not provided supplementary formula had lower odds of developing NAFLD (OR, 0.64), but adolescents born to mothers with prepregnancy obesity had higher odds of developing NAFLD (OR, 2.29).[54] A longitudinal study of 3188 children with laboratory data and 1887 children with follow-up ultrasound data from ages 3 to 13 years in the United Kingdom showed that children with a higher intake of energy, but not specific macronutrients, were more likely to have NAFLD as defined by increased hepatic echogenicity on ultrasound and laboratory evidence of hepatic inflammation in adolescence.[55] Dietary fructose consumption is considered to play an important role in the development of NAFLD through increased serum free fatty acids and deposition of hepatotoxic lipids onto the liver, leading to endoplasmic reticulum and mitochondrial stress.[50] A recent longitudinal, population-based study of 1940 infants in the Netherlands demonstrated an association between higher sugar-containing beverage intake in infancy with NAFLD in school-aged children independent of sugar-containing beverage intake and BMI at school age.[56]

Sleep

Numerous studies have investigated the impact of sleep on obesity and NAFLD. Disruption in circadian rhythm has been proposed as a potential risk factor for the development of NAFLD. Circadian rhythm disruption is hypothesized to disturb multiple metabolic regulatory genes that are synchronized with the circadian clock.[57] This was supported in a mouse model of clock gene knockout mice that developed hepatic steatosis when fed a standard diet and developed severe hepatic steatosis when fed a high-fat diet.[58] Furthermore, wild-type mice raised in chronic sleep deprivation conditions developed hepatic steatohepatitis and fibrosis.[59] In a meta-analysis in children, short sleep duration was associated with increased risk of obesity.[60] Therefore, counseling on healthy sleep patterns in children may be an additional lifestyle intervention for pediatricians treating children with obesity and NAFLD. Additionally, obstructive sleep apnea (OSA) is highly associated with NAFLD.[61] Data from a study of 31 adolescents with biopsy-proven NAFLD who underwent polysomnography suggest that children with NAFLD and OSA may trend toward more severe fibrosis (P=.08), and that increased sleep hypoxia as measured by SaO_2 less than 90% in children with NAFLD and sleep apnea is associated with higher hepatic steatosis (P=.0008), histologic grade of inflammation (P=.04), and NAFLD Activity Score (NAS) (P=.055).[62]

Evaluation and Diagnosis

Currently, NAFLD remains a diagnosis of exclusion and relies on liver biopsy for definitive diagnosis. Histologically, the pattern of pediatric NAFLD can differ from the pattern of adult NAFLD. In children, NAFLD shows

2 patterns. Type 1 shares features with classic NASH described in obese adults, with centrilobular intracellular lipid droplets with neutral lipid accumulation. Type 1 is also associated with hepatocellular ballooning, lobular inflammation, and perisinusoidal fibrosis. Type 2 NAFLD is characterized by steatosis with portal inflammation and sometimes periportal fibrosis. Type 2 NAFLD is seen more commonly in males of Hispanic or Asian descent. Although there can be an overlap of histologic features, type 2 NAFLD is the pattern seen more commonly in children.[63]

Noninvasive biomarkers and imaging techniques have become important tools in the management of children, given the slowly progressive natural history of NAFLD and the risks associated with anesthesia and liver biopsy. Several serum biomarkers for steatohepatitis have been studied in adult and pediatric populations; however, none are validated and routinely used in pediatric clinical practice at this time.[64] Serum biomarkers for hepatic fibrosis, such as the NAFLD Fibrosis Score (NFS) and Fibrosis-4 (FIB-4) index, have been extensively studied in the adult population with NAFLD.[65] A large meta-analysis comparing imaging and laboratory tests to detect fibrosis in 13,046 adults with biopsy-proven NAFLD found that the sensitivity of the FIB-4 index in detecting advanced fibrosis was 64.4% (54.4%-77.8%), 65.5% (60.9%-70.1%) for NFS, and 44.3% for the BARD score.[66] An additional meta-analysis of 4 studies with 1038 adult patients with NAFLD and 135 patients with advanced fibrosis comparing the FIB-4 index, NFS, and the BARD score found that the FIB-4 index with a 1.30 cutoff has better diagnostic accuracy than the FIB-4 index with a 3.25 cutoff, NFS, and the BARD score.[67] In a study comparing the performance of the AST/ALT ratio, AST to Platelet Ratio Index (APRI), NFS, and FIB-4 index adult hepatic fibrosis scores to predict hepatic fibrosis among 92 children (mean age of 13 years) with biopsy-proven NAFLD, Mansoor and colleagues found generally poor performance and concluded that adult-based fibrosis scores did not have acceptable parameters to apply to children.[68] The Pediatric NAFLD Fibrosis Score (PNFS) was developed and validated in a large tertiary center among 242 children (the majority of whom were white) with biopsy-proven NAFLD using ALT, alkaline phosphatase, platelet counts, and γ-glutamyltransferase (GGT).[69] PNFS was found to have an area under the receiver operating characteristic (AUROC) curve of 0.74 and had better test performance measures to detect fibrosis in children than the APRI, NAS, and FIB-4 index. However, external validation of this scoring system using more diverse pediatric populations is needed. A recent study of 146 children with biopsy-proven NAFLD enrolled in the NASH-CRN study CyNCh (Cysteamine Bitartrate Delayed-Release for the Treatment of NAFLD in Children) showed that dynamic changes in ALT and GGT over 52 weeks were correlated with histologic changes as scored by NAS and, therefore, may be indicators of treatment response.[70] However, this model has not been widely validated in clinical practice.

Vibration-controlled transient elastography (VCTE; FibroScan, Echosens) is a noninvasive, ultrasound-based point-of-care test. VCTE produces a liver stiffness measurement (LSM, measured in kilopascals [kPa]), which estimates the degree of hepatic fibrosis, and measures controlled attenuation parameter (CAP, measured in decibels/meter), which is an estimate of hepatic steatosis. CAP measurements have been shown to correlate with steatosis in children with NAFLD.[71] In a study of 393 adults with biopsy-proven NAFLD, a LSM of 5.6 kPa had a high sensitivity to diagnose NAFLD with a sensitivity of 0.9, specificity of 0.44, positive predictive value of 0.62, and negative predictive value of 0.81. A LSM of 12.1 kPa had a high sensitivity for cirrhosis with a sensitivity of 0.9, specificity of 0.82, positive predictive value of 0.34, and negative predictive value of 0.99.[72] Validated LSM cutoffs correlate to advanced fibrosis in children with chronic liver disease, which suggests that VCTE may be a useful tool for the detection of both steatosis and fibrosis in children.[72] Because only 11% of this study's participants had NAFLD, more NAFLD-specific studies would be helpful.[73] In a study of 52 consecutive children with biopsy-proven NASH (mean age of 13 years), a LSM cutoff of less than 5.1 kPa was able to estimate any degree of liver fibrosis (≥F1) with an AUROC curve of 0.97. Similarly, a LSM of less than 7.5 kPa had an AUROC curve of 0.99 to estimate significant fibrosis (≥F2), and a LSM of less than 9 kPa had an AUROC curve of 1 to estimate advanced fibrosis (≥F3).[74] However, it has been found that severe steatosis may falsely elevate LSM in patients with NAFLD, therefore suggesting a more severe degree of hepatic fibrosis than actually present.[75]

Magnetic resonance imaging (MRI) and magnetic resonance elastography (MRE) are other imaging-based, noninvasive tools in the diagnosis and monitoring of pediatric NAFLD. A study of 174 children (mean age of 14 years) demonstrated that MRI estimates of liver proton density fat fraction correlated well with steatosis grade on liver histology (P<.01).[76] MRE can also quantify hepatic fibrosis. A study of 90 children who were enrolled in the NASH-CRN study and who had undergone MRE and liver biopsy showed that MRE had an accuracy of 88.9%, 90.0%, and 86.7% across the 3 study centers.[77] However, MRE is limited by the number of pediatric centers that offer it, high cost, and possible need for anesthesia in younger children.[65] Given the number of limitations to both serum and imaging noninvasive biomarkers for

NAFLD, liver biopsy remains the gold standard for diagnosis of NAFLD.

Management

The current management strategy for children with NAFLD involves lifestyle changes to decrease total ingested energy and physical activity to increase daily expended energy. In adults, weight loss of greater than or equal to 10% of total body weight is associated with regression of hepatic fibrosis.[78] Physical activity plays an important role in both the development and treatment of NAFLD. In adults, no or low amounts of physical activity have been shown to increase the risk of the development of NAFLD, and moderate amounts of physical activity have been shown to increase odds of improvement in NAFLD.[79] A randomized controlled trial (RCT) showed that a 3-month intervention period of aerobic and resistance exercise had a statistically significant larger reduction in intrahepatic fat independent of caloric restriction compared with no exercise in obese adolescent boys 12 to 18 years of age (P<.05).[80] This study was not specific to children with NAFLD but supports the role of exercise in improving intrahepatic fat. In a meta-analysis of 19 studies including 923 patients, lifestyle changes to treat NAFLD in children showed significant improvements in BMI, aminotransferase levels, and hepatic steatosis.[81]

In terms of lifestyle interventions, research has focused on the impact of processed sugars and fats. In a recent RCT, 40 adolescent boys with a clinical pathologic diagnosis of NAFLD with active disease as defined by MRI measures of steatosis and ALT greater than 45 U/L were randomized to menu planning with sugar-free meals provided by the study for the boys' entire household, with sugar restricted to less than 3% of total calories vs usual diet in the control group for 8 weeks. Boys randomized to the low-sugar diet showed a statistically significant larger improvement in hepatic steatosis as measured by MRI (-6.23%; 95% CI, -9.45% to 3.02%; P<.001) and improvement in ALT (103 to 61 U/L vs 82 to 75 U/L; P<.001).[82] There is also interest in researching the Mediterranean diet, given its predominant macronutrients. A RCT studying the Mediterranean diet in adults has shown potential for improvement in clinical parameters such as increased weight loss, greater improvement in ALT and liver stiffness, and higher adherence when receiving repeated nutritional counseling compared with a control group of overweight or obese adults with NAFLD.[83] A single-arm, unblinded cohort study examining specific polyunsaturated fatty acids (PUFAs) in 20 obese children and adolescents with elevated hepatic fat fraction measured by MRI demonstrated that obese youth with NAFLD randomized to a low n-6:n-3 PUFA ratio normocaloric diet led to a greater reduction in ALT (P=.001), triglycerides (P=.046), and insulin sensitivity as measured by insulin concentrations during oral glucose challenge tolerance test (P=.045) independent of weight loss.[84] The potential for n-3 PUFA supplementation to reduce hepatic steatosis in children with NAFLD has been shown; however, there are no longer-term studies to further support a recommendation in regard to supplementation with n-3 PUFA at this time.[85]

No medications are currently approved by the US Food and Drug Administration (FDA) for the treatment of NAFLD in children.[19] The TONIC (Treatment of NAFLD in Children) trial was a phase 3, multicenter, randomized, double-blinded, placebo-controlled trial evaluating vitamin E or metformin in 173 children ages 8 to 17 years with biopsy-proven NAFLD that showed that metformin or vitamin E was not superior to placebo in improvement in ALT or liver histology. Daily vitamin E (800 IU) was shown to have an improvement in the study's secondary endpoint of resolution of NASH in children with biopsy-proven NASH compared with placebo (P=.006).[86]

There is increasing interest in the NAFLD literature regarding the role of the microbiome in NAFLD.[87] Therefore, several studies have been designed to assess whether probiotics have a meaningful effect on the natural history of NAFLD. In 2017, a RCT completed in Iran included 64 obese children ages 10 to 18 years with clinically diagnosed NAFLD who were randomized to receive a probiotic (PRO-Kids [Hyperbiotics], which included strains of *Lactobacillus acidophilus, Bifidobacterium lactis, Bifidobacterium bifidum,* and *Lactobacillus rhamnosus*) vs placebo for 12 weeks. The probiotic group had statistically significant improvement in transaminases, low-density lipoproteins, and triglycerides without a significant change in BMI or weight.[88] In a meta-analysis of the current research on the role of probiotics as a treatment for NAFLD in all age groups, probiotics were shown to improve hepatic steatosis and LSM; however, there was high heterogeneity among the studies.[89] A RCT in adults ages 25 to 70 years with imaging or biopsy-proven NAFLD randomized to 10 weeks of twice-daily VSL#3 (VSL Pharmaceuticals) vs placebo failed to show improvements in biomarkers of liver injury and cardiovascular risk as measured by serum biomarkers of endothelial function and oxidative stress in patients with NAFLD compared with placebo.[90] Therefore, additional RCTs are needed to further define the efficacy of probiotics to treat NAFLD.[89]

Therapeutic Pharmacologic Targets

Significant advances are being made to develop therapeutic targets to treat NASH beyond lifestyle changes to

promote weight loss.[91] Many pathways can be targeted by pharmacologic treatment, including cell death (antioxidants such as vitamin E), metabolism (glucagon-like peptide-1 receptor agonists such as liraglutide [Novo Nordisk]), gut-liver axis (fibroblast growth factor-19 agonists such as NGM282 [NGM Biopharmaceuticals]), profibrotic pathways (lysyl oxidase homolog 2 inhibitors such as simtuzumab [Gilead Sciences]), and inflammation (CC chemokine receptors type 2 and 5 inhibitors such as cenicriviroc [Takeda]).[92-97] There had been promising results from a phase 3 clinical trial on the use of obeticholic acid (Ocaliva, Intercept Pharmaceuticals) to resolve advanced fibrosis in adults with NASH; however, as of October 2021, the FDA has not yet approved this medication.[98] Currently, drug development for the treatment of NASH is a large and active area of interest and is focused on adults and children. According to ClinicalTrials.gov, a phase 2 trial of losartan in children with NAFLD has been completed but not yet published (NCT03467217). However, many of these potential drugs have not been shown to be effective in the most common primary endpoint of regression or resolution of hepatic fibrosis from NAFLD.[93] As many drugs are currently in different developmental stages, clinicians await the results of clinical trials and look forward to future therapeutic options for children who have NAFLD.

Conclusion

NAFLD is the most common liver disease in the world and has increased in incidence over the past decade and will likely increase further.[6] Additionally, advances in the understanding of the pathophysiology, natural history, diagnosis, and evaluation of children with NAFLD are needed to optimize the care of children with the most common cause of chronic liver disease.

Given that NAFLD has been associated with the need for liver transplantation in adulthood, it is imperative that children with NAFLD be identified and treated prior to the development of NASH and progression to severe liver disease. While the current treatment continues to be primarily lifestyle modification in children, new diagnostic and therapeutic options may be available to children with NASH in the future.

Disclosures

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