Nonalcoholic Fatty Liver Disease in Children

Hepatic and Extrahepatic Complications

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KEYWORDS

• Nonalcoholic fatty liver disease • Extrahepatic complications
• Hepatic complications • Metabolic syndrome • Obesity complications in children

KEY POINTS

- Nonalcoholic fatty liver disease (NAFLD) includes a broad spectrum of liver diseases ranging from simple steatosis to nonalcoholic steatohepatitis with further progression to fibrosis or cirrhosis.
- Liver biopsy still remains the gold standard for the diagnosis of NAFLD.
- Noninvasive diagnostic methods, such as serum markers or imaging, are still not well established or validated for children with NAFLD.
- NAFLD is associated with multiple extrahepatic complications, such as cardiovascular disease, type 2 diabetes, sleep disorders, and osteoporosis.
- Clinicians should be aware of these extrahepatic complications to ensure prompt screening and treatment.

INTRODUCTION

With the increasing trend in obesity, nonalcoholic fatty liver disease (NAFLD) has now become the most common cause of chronic liver disease in children and adolescents, with a prevalence of 3% to 10% in the general pediatric population increasing to up to 70% in obese children.[1,2] NAFLD is a clinicopathologic entity that encompasses a broad spectrum of liver injury ranging from accumulation of fat in the liver (simple

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steatosis) to the potentially progressive form of nonalcoholic steatohepatitis (NASH) characterized by hepatocyte ballooning and inflammation, and is often associated with fibrosis. NAFLD can cause decompensated cirrhosis requiring liver transplantation and hepatocellular carcinoma even in children.[3–5]

Although NAFLD increases the risk of liver-related mortality and morbidity, the most common causes of death among patients with NAFLD are cardiovascular disease (CVD) and extrahepatic malignancy.[6] This has led to an increasing awareness of extrahepatic complications associated with NAFLD. NAFLD is often considered a hepatic manifestation of metabolic syndrome (MetS); however, emerging data indicate that NAFLD can be a risk factor for the development of MetS, type 2 diabetes mellitus (DM), and CVD.[7–9] Similarly, NAFLD is shown to be associated with other extrahepatic complications, such as chronic kidney disease, hypothyroidism, polycystic ovarian syndrome, obstructive sleep apnea (OSA), osteoporosis, and colorectal cancer in adults.[10,11] In children, recent evidence suggests that pediatric NAFLD is associated with individual extrahepatic complications, such as CVD, type 2 DM, retinopathy, vitamin D deficiency, and low bone mineral density.

HEPATIC COMPLICATIONS

Clinical Manifestations

Children with NAFLD are usually diagnosed because of incidental elevation in liver enzymes or evidence of steatosis on ultrasound done either as a part of routine screening test in obese children or for evaluation of other diseases. Children remain asymptomatic and present clinically once the liver disease has progressed or with concurrent extrahepatic manifestations of MetS. The mean age of diagnosis of NAFLD in children is reported to be between 11 and 13 years.[12] Clinical manifestations of NAFLD include nonspecific right upper quadrant abdominal pain from stretching of liver capsule (approximately 42%–59% of the patients), fatigue, and irritability. Physical examination may reveal acanthosis nigricans from insulin resistance (IR); hepatomegaly in up to 50% of the patients, which might be difficult to assess because of abdominal obesity; and, rarely, splenomegaly.[13,14]

Diagnostic Methods

Liver enzymes

In spite of the high prevalence of NAFLD in children, screening and diagnostic approaches in pediatric NAFLD are not well defined. The American Academy of Pediatrics recommends biannual screening of children 10 years of age or older who are overweight with other risk factors for NAFLD or obese even without risk factors with alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels and further referral to pediatric hepatologist if ALT or AST levels are 2 times the upper limit of normal levels.[15] However, the European Society for Pediatric Gastroenterology Hepatology and Nutrition recommends screening in obese children 3 years of age or older with both liver enzymes and ultrasound.[14] Analysis of data from the National Health and Nutrition Examination Survey between 1999 and 2006 in the SAFETY study showed that the 95th percentiles for ALT in healthy weight, metabolically normal, and liver disease–free children were 26 U/L in boys and 22 U/L in girls in comparison with the median upper limit of normal of 53 U/L (range 30–90 U/L) used at different children's hospitals in the United States.[16] Hence, lower cutoff of ALT to screen for NAFLD should be used to improve its sensitivity.

Imaging

Ultrasound is a widely used screening tool for hepatic steatosis with a sensitivity of approximately 80% and specificity of approximately 50% to 60%.[17,18] However, ultrasound has decreased sensitivity in patients with mild steatosis.[19] Moreover, ultrasound cannot accurately distinguish between simple steatosis and NASH or fibrosis. Newer imaging techniques, such as controlled attenuation parameter and MRI with proton density fat fraction, are shown to be more accurate in assessing hepatic steatosis.[20,21] Imaging techniques that measure liver stiffness using elastography to assess hepatic fibrosis have been developed recently.[22] Although these recent imaging techniques are more accurate than conventional ultrasound, their use is currently limited because of cost and the lack of validated cutoff values in children.

Liver biopsy

Liver biopsy remains the gold standard in the evaluation of steatosis, NASH, and NAFLD-related liver fibrosis. Simple steatosis is defined as macrovesicular steatosis in $\geq$5% of the hepatocytes after excluding other causes of hepatic steatosis, such as viral hepatitis, Wilson disease, or autoimmune hepatitis.[23] NASH is characterized by hepatocyte injury (ballooning) and neutrophilic infiltration of the liver (lobular and portal inflammation). In a retrospective analysis of children with biopsy-proven NAFLD, 2 distinctive patterns of histology were identified. Steatosis, ballooning degeneration, lobular inflammation, and perisinusoidal fibrosis were categorized as type 1 (adult type) NASH, whereas steatosis, portal inflammation, and portal fibrosis were categorized as type 2 (pediatric type) NASH. Type 2 NASH was found to be the most common histologic pattern seen in younger children with NAFLD.[24]

Progression of Liver Disease

Limited data exist on pediatric NAFLD progression from simple steatosis to NASH, to fibrosis and cirrhosis. The presence of advanced liver fibrosis is shown to be a predictor of overall and liver-related mortality irrespective of other histologic features.[25] The prevalence of advanced liver fibrosis in children with NAFLD is variable. In a study by Alkhouri and colleagues,[26] only 15% of 67 children with biopsy-proven NAFLD were found to have significant fibrosis (stage 2–3). In a retrospective review of liver histology from 742 children who had autopsy for sudden expected death, NASH was observed in approximately 23% of the children with fatty liver of which only 9% of them had bridging fibrosis or cirrhosis.[27] In a multicenter retrospective cohort study including 108 children with biopsy-proven NAFLD, stage 3 fibrosis was observed in approximately 20% of the children at the time of presentation.[28] In another multicenter study involving 92 children with biopsy-proven NAFLD, approximately 24% of them had stage 3 fibrosis.[29] Therefore, approximately 10% to 25% of children diagnosed with NAFLD can progress to advanced fibrosis.

Long-term follow-up studies to assess liver and overall outcomes in children with NAFLD are lacking. A retrospective longitudinal follow-up of 66 children with NAFLD over 20 years demonstrated a standardized mortality ratio of 13.6 of whom 3% of them needed liver transplantation (LT). The observed LT-free survival was significantly lower than expected survival of the US population of same age and gender.[3] In a data analysis from United Network for Organ Sharing database of 330 children and young adults who underwent LT for NASH cirrhosis between 1987 and 2012, 14 patients had LT when younger than 18 years, 20 had LT between 18 and 25 years of age, and 13 needed re-transplantation due to NASH recurrence.[4] Therefore, it is very clear that

pediatric NAFLD can progress to end-stage liver disease requiring LT in childhood and young adults.

Multiple adult studies have shown that NAFLD is a risk factor for the development of hepatocellular carcinoma (HCC) even in the absence of cirrhosis.[30] One of the follow-up studies involving adults with cirrhosis showed that the yearly cumulative incidence of HCC in patients with NASH cirrhosis was 2.6%.[31] HCC has been reported in a pediatric patient in the setting of obesity and steatosis without evidence of fibrosis or cirrhosis.[5] Pediatric NAFLD might lead to increased risk of HCC in adulthood, but this association has not been studied. Development of HCC in the absence of cirrhosis or fibrosis might indicate the potential role of other factors, such as metabolic syndrome, obesity, IR, or oxidative stress in the pathogenesis of HCC in patients with NAFLD.[32]

EXTRAHEPATIC COMPLICATIONS

Mechanisms involved in the development of extrahepatic complications in children with NAFLD are not completely understood. It is hypothesized to be caused by an interplay of many factors such as proinflammatory mediators, oxidative stress, IR, and lipotoxicity. Different studies evaluating different extrahepatic complications (**Fig. 1**) of pediatric NAFLD are outlined in **Table 1**.

Cardiovascular Disease

In recent years, there has been a tremendous interest in understanding the association between NAFLD and CVD and potential role of NAFLD in the pathophysiology of

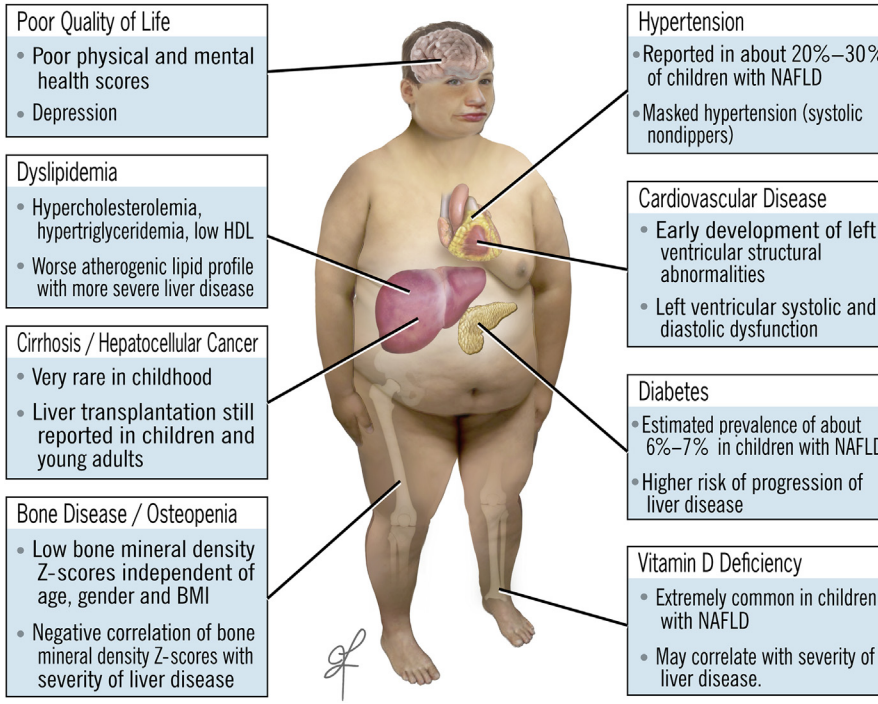

Fig. 1. Extrahepatic complications in children with NAFLD. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2016. All Rights Reserved).

Table 1
Studies of extrahepatic complications in children with NAFLD

References	Study Population	Diagnosis of NAFLD	Variable of Interest	Results
Cardiovascular diseases				
Schwimmer et al,[37] 2008	Obese children with (n = 150) and without NAFLD (n = 150)	Liver biopsy	Dyslipidemia Impaired fasting glucose Hypertension	Children with NAFLD had significantly higher TC, LDL-C, TG, fasting glucose and blood pressures than those without NAFLD.
Nobili et al,[39] 2010	Children with NAFLD (n = 18)	Liver biopsy	Atherogenic lipid profile	NAFLD activity and fibrosis scores had a significant positive correlation with TG/HDL-C, TC/HDL-C, and LDL-C/HDL-C ratios even after the adjustment for BMI, insulin resistance, impaired glucose intolerance and MetS.
Corey et al,[40] 2015	Children with NAFLD in TONIC trial (n = 173). Children with and without histologic improvement are compared	Liver biopsy	Dyslipidemia	Children with histologic improvement had significant decreases in TC, LDL-C and non-HDL-C compared with children with no histologic improvement.
Pacifico et al,[41] 2008	Obese children with (n = 29) and without NAFLD (n = 33) and lean subjects (n = 30)	Liver ultrasound	CIMT	CIMT was significantly higher in obese children with NAFLD compared to age-matched and sex-matched obese children without NAFLD and healthy controls. There was also a significant association between higher CIMT and severity of hepatic steatosis.

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References	Study Population	Diagnosis of NAFLD	Variable of Interest	Results
Demircioğlu et al,[42] 2008	Study groups: Controls (n = 30) Obese children without hepatic steatosis (n = 26) Obese children with grade 1 hepatic steatosis (n = 32) Obese children with grade 2 or 3 hepatic steatosis (n = 22)	Liver ultrasound	CIMT	CIMT was significantly higher in obese children with NAFLD and correlated with grades of steatosis.
Manco et al,[43] 2010	Study groups: Obese children with NAFLD (n = 31) Obese children matched for gender, age and BMI without NAFLD (n = 49)	Liver biopsy	CIMT	There was no significant association between CIMT and NAFLD or grades of steatosis.
Schwimmer et al,[44] 2014	Children with NAFLD (n = 484) from NASH CRN Children assessed both at enrollment and 48 wk afterward	Liver biopsy	Hypertension	Prevalence of hypertension was approximately 36% at baseline and 21% at 48-wk follow-up. Children with hypertension had more severe grades of steatosis than children without hypertension. Girls with NAFLD had higher risk of having persistent hypertension at 48-wk follow-up.

Giordanno et al,[45] 2014	Children with NAFLD (n = 101)	Liver biopsy	Systolic and diastolic dipping by ambulatory blood pressure monitoring	Systolic nondippers had significantly impaired oral glucose tolerance and higher insulin resistance compared with systolic dippers.
Sert et al,[46] 2012	Obese adolescents with and without NAFLD (n = 80) Lean subjects (n = 37)	Liver ultrasound and ALT	Left ventricular mass	Significantly higher left ventricular mass with impaired diastolic function in obese children with NAFLD compared with obese children with no NAFLD and lean subjects.
Pacifico et al,[47] 2014	Obese children with (n = 54) and without (n = 54) NAFLD. Lean healthy subjects (n = 18)	MRI	Left ventricular function	Obese children with NASH had more severe left ventricular systolic and diastolic dysfunction compared with obese children with simple steatosis and obese children with no NAFLD.
Fintini et al,[48] 2014	Children with NAFLD (n = 50)	Liver biopsy	Cardiac function and geometry	Left ventricular hypertrophy, concentric remodeling and left atrial dilatation were seen in 50 children with biopsy-proven NAFLD. Significantly lower cardiac alterations in children with simple steatosis compared with those with NASH.
Type 2 DM and abnormal glucose metabolism				
Manco et al,[53] 2008	Children with NAFLD (n = 120)	Liver biopsy	MetS	Prevalence of type 2 DM was approximately 2% in children with NAFLD. Significant association was found between histologic severity and component of MetS.
Schwimmer et al,[54] 2003	Children with NAFLD (n = 43)	Liver biopsy	Insulin resistance Type 2 DM	Insulin resistance was present in 95% of subjects and prevalence of type 2 DM was found to be 14%.
Carter-Kent et al,[55] 2009	Children with NAFLD (n = 130)	Liver biopsy	Type 2 DM	Prevalence of type 2 DM was approximately 7% in children with NAFLD.

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References	Study Population	Diagnosis of NAFLD	Variable of Interest	Results
Xanthakos et al,[56] 2015	Adolescents undergoing bariatric surgery (n = 148)	Liver biopsy	Type 2 DM	Prevalence of type 2 DM was found to be approximately 14% and diabetes was found to be the only significant predictor of presence of liver fibrosis.
Newton et al,[57] 2016	Children with NAFLD (n = 675)	Liver biopsy	Prediabetes Type 2 DM	Prevalence of prediabetes and diabetes were 23.4% and 6.5%, respectively. Girls with NAFLD had higher risk of developing prediabetes and type 2 DM than boys with NAFLD. Children with prediabetes and diabetes had significantly higher odds for developing NASH.
Vitamin D deficiency				
Nobili et al,[61] 2014	Children with NAFLD (n = 73)	Liver biopsy	Vitamin D deficiency	Children with NASH had significantly lower vitamin D levels than those without NASH. Low vitamin D levels also correlated with the severity of liver fibrosis.
Hourigan et al,[62] 2015	Children with NAFLD (n = 102)	Liver biopsy	Vitamin D deficiency	Prevalence of vitamin D deficiency and insufficiency was high in patients with NAFLD. There was no relationship between vitamin D levels and histologic severity of NAFLD.
Osteopenia and osteoporosis				
Pirgon et al,[64] 2011	Obese children with or without NAFLD (n = 82) Lean controls (n = 30)	Liver ultrasound	BMD	Children with hepatic steatosis on ultrasound had lower spine BMD Z-scores compared with children with no hepatic steatosis.
Pardee et al,[65] 2012	Obese children with (n = 38) and without (n = 38) NAFLD Age, gender, weight, and height matched	Liver biopsy	BMD	BMD Z-scores are significantly lower in obese children with NAFLD compared with those without NAFLD. Children with NASH had lower BMD Z-scores than those without NASH.

Pacifico et al,[66] 2013	Obese children with (n = 44) and without (n = 44) NAFLD Age, gender, pubertal stage and BMI matched	MRI Liver biopsy in a subset of NAFLD patients	BMD	Obese children with NAFLD had lower BMD Z-scores than those without NAFLD. Children with NASH had lower BMD than those without NASH.
OSA				
Sundaram et al,[68] 2014	Obese children with NAFLD (n = 25)	Liver biopsy	OSA	Prevalence of OSA was approximately 60%. OSA is associated with severe hepatic fibrosis.
Nobili et al,[69] 2014	Obese children with NAFLD (n = 65)	Liver biopsy	OSA	Approximately 60% of the children with NAFLD had OSA. OSA was associated with presence of NASH and fibrosis.
QOL				
Kistler et al,[72] 2010	Obese children with NAFLD (n = 240) Healthy controls (n = 5480)	Liver biopsy	QOL	39% of children with biopsy-proven NAFLD had impaired QOL scores. Children with NAFLD had worse total, physical, and psychosocial scores compared with healthy children.
Kerkar et al,[73] 2013	Children with NAFLD (n = 48) Obese controls without NAFLD (n = 40)	At least 3 of the following: BMI >97th percentile ALT >50 IU/L, positive liver ultrasound Liver biopsy	QOL	Children with NAFLD had higher levels of depression compared with obese controls without NAFLD.

Abbreviations: ALT, alanine aminotransferase; BMD, bone mineral density; BMI, body mass index; CIMT, carotid intima media thickness; CRN, Clinical Research Network; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MetS, metabolic syndrome; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; OSA, obstructive sleep apnea; QOL, quality of life; TC, total cholesterol; TG, triglycerides.

cardiovascular changes. Evidence from multiple studies in adults suggest that NAFLD is an independent risk factor for CVD and has been found to be associated with endothelial dysfunction, increased carotid intima thickness, and higher prevalence of coronary artery plaques.[33–36] However, studies evaluating CVD in pediatric NAFLD are limited. In a case-control study, obese children with biopsy-proven NAFLD had significantly higher total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), fasting glucose, and blood pressure than children with obesity alone, indicating a higher cardiovascular risk profile in children with NAFLD.[37]

Atherosclerosis can begin as early as in childhood, with the deposition of fatty streaks in the coronary and carotid arteries.[38] Assessment of subclinical atherosclerosis and CVD risk in children can be accomplished with lipid profile and examination of vascular structures, such as carotid intima media thickness (CIMT) or endothelial dysfunction. In a study that recruited consecutive children with biopsy-proven NAFLD, Nobili and colleagues[39] found that NAFLD activity and fibrosis scores had a significant positive correlation with TG/HDL-C, TC/HDL-C, and LDL-C/HDL-C ratios even after the adjustment for body mass index (BMI), IR, impaired glucose intolerance, and MetS. This positive correlation between atherogenic profile and histologic severity has also been demonstrated in data analysis from the Treatment of NAFLD in Children (TONIC) trial. Children with histologic improvement in the TONIC trial had significant decreases in TC, LDL-C, and non–HDL-C compared with children with no histologic improvement.[40]

Many studies have assessed CIMT in children with NAFLD with contradictory results. A case-control study demonstrated that CIMT was significantly higher in obese children with NAFLD diagnosed with ultrasound compared with age-matched and sex-matched obese children without NAFLD and healthy controls. There was also a significant association between higher CIMT and severity of hepatic steatosis.[41] Similar results were also found in another prospective case-control study.[42] Conversely, a more recent case-control study involving age, BMI, and sex-matched obese children with and without biopsy-proven NAFLD reported no significant association between CIMT and NAFLD.[43] These differences in results could be from different study designs, research methodologies, and small sample sizes.

Children with NAFLD are also reported to have hypertension as a part of the metabolic syndrome. In a longitudinal study including 382 children with biopsy-proven NAFLD, prevalence of hypertension was approximately 36% at baseline and 21% at 48-week follow-up. Children with hypertension had more severe grades of steatosis than children without hypertension. Girls with NAFLD had higher risk of having persistent hypertension at 48-week follow-up.[44] Ambulatory blood pressure monitoring performed in 101 children with biopsy-proven NAFLD in a study by Giordano and colleagues[45] showed significant impaired glucose tolerance and IR in systolic nondippers compared with systolic dippers.

Multiple pediatric studies have consistently demonstrated a significant association between NAFLD and structural and functional abnormalities of the heart. Sert and colleagues[46] reported significantly higher left ventricular mass with impaired diastolic function in obese children with NAFLD compared with obese children with no NAFLD and lean subjects. Few studies also have reported positive correlation between cardiac dysfunction and histologic severity. Doppler echocardiography in 108 obese children in a study by Pacifico and colleagues[47] showed more severe left ventricular systolic and diastolic dysfunction in obese children with NASH compared with obese children with simple steatosis and obese children with no NAFLD. Similarly Fintini and colleagues[48] reported left ventricular hypertrophy, concentric remodeling, and left atrial dilatation in 50 children with biopsy-proven

NAFLD with significantly lower cardiac alterations in children with simple steatosis compared with those with NASH.

Type 2 Diabetes Mellitus and Abnormal Glucose Metabolism

IR plays an important role in the pathogenesis of NAFLD and therefore abnormal glucose metabolism is very frequent among patients with NAFLD. Multiple adult studies reported significantly higher odds of developing type 2 DM in patients with NAFLD.[10] Type 2 DM is also proven to be an independent risk factor for the progression of NAFLD to NASH and advanced fibrosis.[49] Hepatic steatosis in children has been shown to increase the risk of IR and glucose dysregulation.[50,51]

Although metabolic syndrome and IR are more prevalent in children with NAFLD,[37,52] prevalence of type 2 DM or prediabetes in children with NAFLD is not well established. The prevalence of type 2 DM in a group of 122 children with biopsy-proven NAFLD was found to be approximately 2% in a study by Manco and colleagues.[53] A retrospective review of 43 children with biopsy-proven NAFLD found the prevalence of type 2 DM to be approximately 14%.[54] In another retrospective multicenter study including children with biopsy-proven NAFLD, prevalence of type 2 DM was approximately 7%.[55] These studies were limited by small sample size, lack of correlation with histologic severity, and cross-sectional nature of the study. The relationship between prevalence and histologic severity was addressed by a prospective multicenter cohort study including adolescents undergoing bariatric surgery. In this study, overall prevalence of diabetes was found to be approximately 14%, but more importantly, diabetes was found to be the only significant predictor of presence of liver fibrosis (odds ratio = 3.56).[56] This relationship between type 2 DM and histologic severity was confirmed by a more recent multicenter cross-sectional study including 675 children with biopsy-proven NAFLD enrolled in the NASH Clinical Research Network (CRN). In this study, prevalence of prediabetes and diabetes were 23.4% and 6.5%, respectively. Interestingly, girls with NAFLD had higher risk of developing prediabetes and type 2 DM than boys with NAFLD. A key finding is that children with prediabetes and diabetes had significantly higher odds for developing NASH.[57] Thus, recently emerging pediatric studies indicate that type 2 DM is a risk factor for the progression of liver disease in NAFLD with possible increase in liver-related mortality and morbidity. Longitudinal studies are needed to understand the cause-effect relationship between NAFLD and type 2 DM.

Vitamin D Deficiency

Vitamin D deficiency has been associated with obesity in adults[58] and children.[59] Adult patients with NAFLD are found to have a high prevalence of vitamin D deficiency with low levels of vitamin D, correlating with histologic severity of NAFLD.[60] Similarly, pediatric studies also have reported high prevalence in children with NAFLD but correlation with histologic severity is contradictory. In a cross-sectional Italian study including obese and overweight children with biopsy-proven NAFLD, children with NASH had significantly lower vitamin D levels than those without NASH. Moreover, low vitamin D levels also correlated with the severity of liver fibrosis.[61] More recent data analysis from NASH CRN involving children with biopsy-proven NAFLD showed high prevalence of vitamin D deficiency and insufficiency; however, there was no relationship between vitamin D levels and histologic severity of NAFLD.[62] These are cross-sectional studies with limited sample size and lack of healthy controls, so the pathophysiology of vitamin D deficiency in pediatric NAFLD could not be inferred.

Osteopenia and Osteoporosis

Osteoporosis is more frequent in patients with chronic liver disease.[63] There is accumulating evidence to support the impact of NAFLD on bone health in both adults and children.[10] The relationship between bone mineral density (BMD) and pediatric NAFLD was first evaluated in a Turkish study involving obese children with or without hepatic steatosis (diagnosed with liver ultrasound). Children with hepatic steatosis on ultrasound had lower spine BMD Z-scores compared with children with no hepatic steatosis.[64] Pardee and colleagues[65] evaluated BMD in obese children with (biopsy-proven) and without NAFLD and found that BMD Z-scores are significantly lower in obese children with NAFLD compared with those without NAFLD independent of age, gender, ethnicity, weight, and height. Moreover, among children with NAFLD, children with NASH had lower BMD Z-scores than those without NASH. Similar results were demonstrated in a case-control study in which obese children with NAFLD (diagnosed with MRI) had lower BMD Z-scores than age, gender, BMI, and pubertal stage–matched obese children without NAFLD. In a subgroup analysis of children who had biopsy-proven NAFLD, those with NASH had lower BMD than children without NASH.[66] Despite these findings, the role of NAFLD in osteoporosis and risk of fractures in children with NAFLD is not clearly understood due to the lack of longitudinal studies.

Obstructive Sleep Apnea

OSA has been recognized as a risk factor for NAFLD, NASH, and fibrosis independent of age, sex, and BMI in adults.[67] In 2 pediatric studies, polysomnographic evaluation of children with biopsy-proven NAFLD showed a prevalence of approximately 60%. In addition, OSA was significantly associated with NASH and severity of liver fibrosis.[68,69] It is postulated that progression of NAFLD in the setting of OSA could be either from hypoxemia, which can create an oxidative stress, or alternating hypoxemia and normoxia, which might produce a ischemic-reperfusion type of injury to the liver.[70] OSA can significantly affect children's school performance and activity levels, so it is important to screen for OSA in children with NAFLD.

Quality of Life

With the increasing comorbidities associated with NAFLD, patients with NAFLD can have poor quality of life (QOL). Comparison of QOL data between adults with NAFLD and US population with and without chronic illness showed worse physical and mental health scores in patients with NAFLD. Moreover, lower physical health score were associated with severity of the liver disease among patients with NAFLD.[71] Few pediatric studies have also addressed the psychosocial issues in children with NAFLD. In a study by Kistler and colleagues,[72] approximately 39% of children with biopsy-proven NAFLD had impaired QOL scores and children with NAFLD had worse total, physical, and psychosocial scores compared with healthy children; however, no association was found between QOL scores and histologic severity among children with NAFLD. In another case-control study, children with NAFLD had higher levels of depression compared with obese controls without NAFLD.[73] Poor QOL in pediatric NAFLD can increase the burden of illness in both children and parents. Hence, it is important to screen for psychosocial problems and address them accordingly.

SUMMARY

Although NAFLD is a leading cause of chronic liver disease in children and adolescents in developed countries, several aspects of pediatric NAFLD remain unclear.

Most of the pediatric studies on NAFLD are cross-sectional with limited sample size. This limits our understanding of the natural history of the disease in NAFLD. Despite the significant burden of the disease and its potential of progression to cirrhosis even in children and young adults, well-established screening methods are still lacking. Noninvasive biomarkers and imaging techniques in evaluation of NAFLD are being extensively studied, but validation of these tools is lacking. Furthermore, treatment options for liver-related disease in pediatric NAFLD are limited. Currently, lifestyle modification, including healthy dietary habits, weight loss, and physical activity, remains the only effective treatment method.

Multiple adult and pediatric studies have broadened the spectrum of NAFLD to include numerous extrahepatic complications. Long-term prospective longitudinal studies are needed to understand the complex interplay of factors involved in the development of these extrahepatic complications. Nevertheless, it is important for clinicians to recognize these complications associated with pediatric NAFLD. Proper guidelines for screening of these complications in children with NAFLD should be established, as this might have an effect on the long-term morbidity and mortality of the disease.

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