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Nonalcoholic fatty liver disease as a comorbidity of childhood obesity

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Abstract

Childhood obesity is a worldwide health problem associated with an increase in the prevalence and severity of comorbid conditions including nonalcoholic fatty liver disease (NAFLD). The increasing number of children with NAFLD presents a major public health concern. This review focuses on the recent advancements in the understanding of the epidemiology, diagnosis, histology, pathogenesis and treatment of pediatric NAFLD and highlights ongoing challenges and unmet needs in the area.

Keywords

cardiovascular risk; epidemiology; insulin resistance; metabolic syndrome; nonalcoholic fatty liver disease; noninvasive biomarker; noninvasive imaging; obesity; steatohepatitis

Childhood obesity is a significant health problem that has reached an alarming proportion worldwide. Closely associated with obesity, nonalcoholic fatty liver disease (NAFLD) has become the most common cause of chronic liver disease in children [1,2]. NAFLD is a clinico-pathological diagnosis characterized by the accumulation of macrovesicular fat in hepatocytes in the absence of alcohol consumption. NAFLD encompasses a spectrum of histopathological features ranging from simple steatosis to steatosis with inflammation, ballooning degeneration and pericellular fibrosis (nonalcoholic steatohepatitis, [NASH]) to cirrhosis. Although the natural history of NAFLD in children is unknown, it is believed that

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simple steatosis is largely nonprogressive, while NASH can lead to cirrhosis and/or hepatocellular carcinoma [3]. The only long-term follow-up study of children with NAFLD found that over a 20-year period, the odds ratio of dying or requiring liver transplant was 13.6 ($p < 0.001$) in children with NAFLD [4].

Epidemiology

The prevalence of childhood obesity has significantly increased over the past three decades. The existing population-based prevalence studies suggest that greater than 15% of children in North America, Great Britain, western Europe and Korea are obese [5,6]. The rise in the prevalence of obesity has been accompanied by an increase in obesity-related conditions such as NAFLD. Studies of obese adolescents in Europe, North America and Asia indicate that the prevalence of NAFLD is between 10 and 77% [7–10]. However, because fatty liver is a histological diagnosis, estimating the true prevalence of NAFLD in the general pediatric population has been problematic. Most population-based studies measure alanine aminotransferase (ALT) as a surrogate marker for NAFLD, which lacks both specificity and sensitivity. An autopsy-based study is therefore the only practical means for assessing population-based liver histology. A children's autopsy study in San Diego, CA, USA, estimated the prevalence of NAFLD to be 9.6% in children and adolescents, and approximately one-quarter of these cases presented with NASH [1].

Diagnosis

Despite the prevalence of pediatric NAFLD, the condition is largely underdiagnosed. Since most children with NAFLD are asymptomatic, the diagnosis often depends on the detection of hepatomegaly on physical exam or elevated aminotransferases upon screening. In clinical practice, hepatomegaly is frequently missed on examination of obese children and very few at-risk children are screened for NAFLD. A retrospective study of 715 visits by overweight and obese children at Stanford University, CA, USA, and the University of California, San Francisco, CA, USA, found that only 2% of children in general pediatric clinics were screened for NAFLD [11]. The ability to diagnose NAFLD is further complicated by the low sensitivity of ALT for NAFLD detection. Although a majority of patients with NAFLD have elevated ALT, there are several reports documenting normal serum aminotransferases in the setting of biopsy-proven NAFLD [12–14]. In one cohort of 203 children with biopsy-confirmed NAFLD, 21 to 23% had normal values of ALT, and of those children, 60% had liver fibrosis [15,16]. There is clear selection bias to only biopsy those with elevated serum aminotransferases. Ultimately, liver biopsy with histology is required for definitive diagnosis of NASH. Reliance on biopsy, along with the lack of published guidelines for screening high-risk children, has contributed to the underevaluation and underdiagnosis of NAFLD.

Serum biomarkers & noninvasive screening

Given the prevalence of NAFLD in the population and its potential to progress to cirrhosis, the development of noninvasive screening tools is desirable to aid in the selection of children who should undergo liver biopsy and predict those at increased risk for progression. Reports of numerous noninvasive methods to distinguish between stages of NAFLD and identify fibrosis in adult patients can be found in the literature. However, given that children tend to have lower degrees of fibrosis than adults and frequently exhibit a different pattern of fibrodeposition, adult data cannot reliably be extrapolated to the pediatric population.

Several studies in the pediatric population have identified potential variables associated with more severe NAFLD that might serve as additional criteria in the selection of children who should undergo more extensive evaluation and liver biopsy. In one study of 197 children with biopsy-proven NAFLD, waist circumference was found to be independently associated with

fibrosis [15]. In a separate study conducted at eight centers across the USA, 176 children with biopsy-proven NAFLD were analyzed to identify clinical and biochemical parameters that predict the histological pattern and severity of NAFLD [17]. Increasing levels of aspartate aminotransferase (AST) and γ -glutamyl transpeptidase (GGT) were associated with the severity of fatty liver and were superior to ALT for distinguishing patterns of NAFLD. Increased AST and white cell count and decreased hematocrit were associated with the severity of fibrosis. Higher smooth muscle antibody titers were associated with severity of NAFLD and higher insulin levels were found to be predictive of fibrosis. Despite these significant associations with liver histology, in this study no biomarker was found to have the discriminative power to detect NASH severity in a given individual. Recently, Nobili *et al.* reported on the ability of the enhanced liver fibrosis (ELF) test, an algorithm including three direct markers of fibrosis, to accurately assess the level of fibrosis in a sample of children with NASH [18]. However, the utility of this result in the general pediatric population, or even within the pediatric NAFLD population, is limited by the small and atypical study cohort with unusually low ALT values and minimal fibrosis. Further studies in a more generalized and representative population are required before any recommendations for screening can be made.

Imaging

Liver biopsy remains the gold standard for diagnosis of NAFLD/NASH, however, it is an invasive technique that carries a risk of complications. In the adult population, where the safety of percutaneous liver biopsy has been extensively studied, the rate of major complications (most importantly bleeding) is generally very low and dependent on several factors including patient diagnosis and comorbidities, operator experience, and the use of ultrasound guidance and automated biopsy devices [19–21]. Pediatric percutaneous biopsy series are fewer, but suggest an increased risk of bleeding compared with adults, especially in children with abnormal coagulation tests [22–25]. There are no data specific to children with NAFLD, however, in our experience these children tend to have normal coagulation tests and extremely low rates of biopsy-associated complications. Still, given the cost and potential for complications with liver biopsy, the development of noninvasive imaging techniques to evaluate and longitudinally monitor NAFLD is highly desirable.

Several radiological modalities – including ultrasound (US), magnetic resonance imaging (MRI) and computed tomography (CT) – are currently in clinical use for the assessment of hepatic steatosis, however, none are capable of quantifying the degree of steatosis, staging liver fibrosis or assessing liver-cell injury. Furthermore, the majority of studies testing the utility of these radiological modalities in NAFLD are conducted in adults and there are limited data on the accuracy of imaging procedures in the pediatric population.

Current evidence suggests that MRI is the modality most likely to be useful in the evaluation and monitoring of pediatric NAFLD. MRI offers several approaches for the assessment of NAFLD. Modified phase-shift imaging methods can calculate fat fractions and have been used to accurately measure total liver fat fractions [26–28]. Developing technology using contrast agents has enabled the visualization of liver fibrosis directly [29]. MRI with intravenous contrast and MR elastography can be used to measure liver fibrosis. Furthermore, MRI is rapid (data can be acquired in a single breath-hold), easy to perform and interpret and operator-independent.

Ultrasound is currently the most commonly employed modality used to screen children for suspected fatty liver disease. It has an excellent safety profile, widespread availability, portability and, compared with other modalities, is relatively low cost. US is useful for detecting steatosis greater than 30% on biopsy [30]. However, US has several important limitations: most importantly, it is operator-dependent and its interpretation is subjective. Furthermore, it

is incapable of identifying milder grades of steatosis, has low sensitivities in obese patients (owing to attenuation of the US beam by fat outside the liver) and, thus, has diminished utility in the evaluation or monitoring of NAFLD [31].

Ultrasonic transient elastography (TE) has received increased attention recently as a means to evaluate fibrosis in patients with chronic liver disease. However, in a cohort of children with biopsy-proven NASH, TE was only able to reproducibly identify subjects without fibrosis or with advanced fibrosis [32]. Given its inability to identify subjects with lower degrees of fibrosis, TE will have limited utility in an unselected pediatric population.

Computed tomography is widely used in research studies of adult NAFLD. However, due to risks from ionizing radiation, CT has a limited role in pediatric NAFLD management.

Histopathology

Two histological subtypes have been described in children with NASH [33]. Type 1 NASH, which is consistent with the histological pattern traditionally described in adults, includes a combination of macrovesicular steatosis with ballooning degeneration and/or perisinusoidal fibrosis and polymorphonuclear leukocyte infiltration (Figure 1). Type 2 NASH, which is a unique pattern of injury observed in the pediatric population, is defined by the presence of steatosis with portal inflammation and/or fibrosis and periportal mononuclear leukocyte infiltration in the absence of ballooning degeneration and perisinusoidal fibrosis. These two distinct subtypes of pediatric NAFLD appear to be associated with different demographic and possibly pathophysiological features. Although the clinical implications of these subtypes are uncertain, the identification of a histological pattern unique to the pediatric population underscores the necessity of addressing pediatric NASH as an entity distinct from NASH in adults.

Pathogenesis

Several genetic and environmental factors are likely responsible for NAFLD and its progression from simple steatosis to NASH. The ‘two-hit’ model, which is widely accepted to explain the pathogenesis of NAFLD/NASH, proposes that fat accumulation in hepatocytes is a prerequisite for a second hit that induces fibrosis and inflammation [34]. Fat accumulation in the liver is likely to result from insulin resistance and concomitant impairment of fatty acid metabolism within liver, skeletal muscle and adipose tissue. Dysfunction of various oxidation pathways within the hepatocyte and subsequent overproduction of reactive oxygen species (ROS), may result in the peroxidation of accumulated lipids, inflammation, hepatocellular apoptosis and fibrogenesis.

In studies from North America, Europe and Asia, obesity is consistently identified as a significant risk factor for NAFLD/NASH [8,12,35,36–38]. Higher BMI, significantly and independently of other risk factors, increases the chances of having liver fibrosis in children [38]. As in adults, visceral obesity, which is associated with abdominal obesity, appears to be more influential than total fat mass in predicting fatty liver [39,40]. Visceral fat delivers free fatty acids (FFAs) and adipokines directly to the portal circulation and has been closely associated with insulin resistance, which appears to be a critical factor in the pathogenesis of NAFLD [8,36,39]. One study of obese children identified hyperinsulinemia as the variable most strongly associated with elevated ALT [41]. In the insulin-resistant state, β -oxidation and ApoB synthesis are decreased while *de novo* lipogenesis is increased in the liver. Peripheral insulin resistance promotes high circulating FFAs and increased delivery of FFAs to the liver. The net result is a decreased secretion of triglyceride (TG) from the liver as VLDL and a net accumulation of TG in macrocytic vacuoles (Figure 2).

Mounting evidence, primarily from investigation in animal models, suggests that diet and gut microbiota play an essential role in the pathogenesis of NAFLD. Metagenomic analysis of the human distal gut microbiome reveals a complex ecosystem with 100-fold more genes than in the human genome, involved in a wide variety of metabolic functions that impact host physiology and nutrition [42]. Recently, a twin study demonstrated that the gut microbiota of obese humans is characterized by phylum-level changes, reduced bacterial diversity, and an increased capacity to absorb energy from the diet [43]. Studies in mouse models have similarly demonstrated that compared with lean mice, obese mice have an altered microbiome with an increased capacity to extract energy from the diet [44]. Alterations in the microbial composition of the intestinal microbiome can cause increased mucosal inflammation and, consequently, increased intestinal permeability and the delivery of increased levels of lipopolysaccharide (LPS) or other proinflammatory bacterial products into the portal circulation, resulting in activation of Kupffer cells and the triggering of an inflammatory cascade. It has recently been reported that chronic consumption of fructose in mice results in increased endotoxin levels in portal plasma, hepatic lipid accumulation and hepatomegaly, all of which are markedly reduced by treatment with nonresorbable antibiotics [45].

It has been proposed that increased consumption of fructose in soft drinks and fruit drinks may have a role in the pathogenesis of NAFLD. Fructose is lipogenic and has been associated with insulin resistance, hepatic steatosis and increased oxidative stress in animal models [46]. In one study, children with biopsy-proven NAFLD were shown to have significantly elevated plasma TG levels and oxidative stress levels after consumption of fructose as compared with glucose [47]. Children without NAFLD, however, were found to have no difference in TG or oxidative stress levels following the consumption of glucose compared with fructose.

The presence of obesity and related insulin resistance do not sufficiently explain why some children develop NAFLD and others do not. A significant genetic component is likely to be involved in the pathogenesis of NAFLD and may explain individual differences in the development of fatty liver. Children from certain ethnicities are predisposed to NAFLD, primarily Hispanics, Asians and Native Americans [1]. Mexican-American children have a higher rate of fatty liver disease even after controlling for the severity of obesity in the population [48]. African-American children, however, have a lower prevalence of NAFLD despite having increased risk factors for fatty liver disease, such as obesity and insulin resistance [48,49]. A familial aggregation study of fatty liver in overweight children with and without NAFLD found that fatty liver is a highly heritable trait. Family members of children with biopsy-proven NAFLD and overweight children without NAFLD were evaluated for fatty liver by MRI [50]. Fatty liver was identified in 17% of siblings and 37% of parents of overweight children without NAFLD and in 59% of siblings and 78% of parents of children with NAFLD. Recent studies have employed genome-wide transcriptional profiling analysis to identify candidate genes that may be causally involved in the pathogenesis of NAFLD [51]. Several genes involved with lipogenesis and inflammation, such as *PPAR-γ*, *SREBF1*, *NFκB*, *TNF-α* and *CASP3*, were found to have significantly altered expression levels in adults with NAFLD and polymorphisms in regulatory cascades may partially explain the heritability factors for fatty liver [51].

NAFLD, the metabolic syndrome & cardiovascular risk factors

The metabolic syndrome (MetS), characterized by central obesity, atherogenic dyslipidemia, impaired glucose tolerance and elevated blood pressure, is a clustering of risk factors for the development of cardiovascular disease and Type 2 diabetes mellitus [52]. Given its strong association with obesity, insulin resistance and dyslipidemia, NAFLD has been regarded as the hepatic manifestation of MetS in adults. The relationship between NAFLD and MetS in children, however, is less studied. It appears that in children there is a strong association

between NAFLD, MetS and cardiovascular risk factors. In fact, the presence or absence of fatty liver may explain why some obese children have MetS and others do not. A case-control study comparing 150 overweight children with biopsy proven-NAFLD to 150 overweight children without NAFLD found significantly higher fasting glucose, insulin, total cholesterol, LDL-cholesterol, TG and systolic and diastolic blood pressure in the children with NAFLD [53]. After controlling for established demographic and biological risk factors, obese and overweight children with MetS were five-times more likely to have NAFLD compared with overweight and obese children without MetS. These findings suggest that fat accumulation in the liver may play a more important role than obesity itself in imposing risk for MetS, Type 2 diabetes mellitus and cardiovascular disease.

Recent studies have proposed a role for fetuin-A – a serum protein produced and secreted by the liver that inhibits insulin-receptor tyrosine kinase activity – as a key link between obesity, insulin resistance, MetS and NAFLD [54]. Obese children with NAFLD have been found to have significantly elevated fetuin-A concentrations compared with obese children without NAFLD and lean controls [55]. Fetuin-A concentrations were shown to be independent of weight status and age, but were significantly correlated with NAFLD and many features of MetS, including elevated blood pressure, waist circumference, insulin resistance and lower HDL-cholesterol. Interestingly, in a group of obese children with NAFLD and elevated fetuin-A concentrations who underwent a 1-year diet and exercise intervention, substantial weight loss was associated with resolution of fatty liver by US and significantly decreased fetuin-A concentrations compared with baseline [55]. Substantial weight loss was also associated with decreased waist circumference, blood pressure, insulin resistance index, insulin and LDL-cholesterol.

The development of NAFLD likely precedes the development of MetS and Type 2 diabetes mellitus. Hepatocyte TG storage has been shown to cause acquired insulin-signaling defects (possibly via fetuin-A) and subsequent insulin resistance, glucose intolerance and Type 2 diabetes mellitus [56]. A long-term follow-up study in adults with biopsy-proven NAFLD found that 9% of subjects had diabetes at baseline and 78% of the subjects had developed impaired glucose tolerance or diabetes after 14 years of follow-up [57]. In children, approximately 8–10% have diabetes at the time that NAFLD is diagnosed [38], while nearly 50% have elevated aminotransferases and suspected fatty liver at the time that Type 2 diabetes is diagnosed [58].

Given its strong association with MetS and cardiovascular risk, the presence of NAFLD in children and adolescents may serve as a marker to stratify the cardiovascular risk of overweight and obese patients. An association between hepatic steatosis and atherosclerotic risk factors is well-described in adult patients [59–63]. In a large study of adults with biopsy-proven NAFLD, carotid intima-media thickness (IMT), a marker of early generalized atherosclerosis, was significantly increased compared with age-, gender- and BMI-matched controls [59]. Carotid IMT was significantly higher for individuals with NASH than for those with simple steatosis, and importantly, the histological severity of NAFLD predicted carotid IMT independently of obesity, insulin resistance and other factors of MetS. A correlation between NAFLD and circulatory endothelial dysfunction has also been demonstrated in adults [64]. Adults with NAFLD demonstrated decreased endothelium-dependent vasodilation, which was significantly associated with the histological severity of NAFLD.

Recent studies in children have demonstrated that NAFLD in the pediatric population is also associated with carotid atherosclerosis and cardiovascular risk. In a study of Japanese University students, those with liver US consistent with fatty liver had increased arterial stiffness as measured by brachial ankle pulse-wave velocity compared with students without evidence of fatty liver [65]. In a study of obese Italian children, those with evidence of fatty

liver on US had greater carotid IMT than obese children without fatty liver [66]. However, given the lack of long-term longitudinal cohort studies in pediatric fatty liver disease, the relationship between the natural history of the disease and the actual risk for future cardiac events is unclear. Whether NAFLD confers additional risk for cardiovascular events beyond its association with traditional cardiovascular risk factors also remains to be determined.

Treatment

The only accepted therapy for pediatric NAFLD is lifestyle modification with diet and exercise. The close association of NAFLD with MetS and obesity in children provides the rationale for the therapeutic role of weight reduction in the treatment of fatty liver disease. Weight-loss-oriented lifestyle interventions in the overweight pediatric population have been shown to increase glucose tolerance and improve the MetS risk-factor profile [67]. In children with presumed NAFLD, several studies demonstrate a normalization of serum aminotransferases associated with weight-loss [9,12,68,69]. Only recently, weight loss in children with NAFLD has also been shown to improve liver histology with a significant decrease in steatosis, inflammation and hepatocyte ballooning in 53 children after 2 years of lifestyle interventions consisting of diet and exercise [68].

To date, several pilot studies of varied design assessing pharmacological treatments for pediatric NAFLD have been reported. Owing to the likely role of insulin resistance and oxidative stress in the development and progression of NAFLD, most studies have focused on the use of metformin or antioxidants. For the most part, efficacy has been modest and results have been disparate. The interpretation of these trials is complicated by small sample sizes, differing definitions for NAFLD between studies and the use of end points other than liver histology to quantify the efficacy of treatment.

Two pediatric treatment trials have evaluated the use of metformin in biopsy-proven NAFLD. The first trial was an uncontrolled open-label study of ten children with biopsy-demonstrated NASH [70]. After 6 months of therapy (metformin 500 mg by mouth twice-daily), all subjects demonstrated significant improvement in ALT and hepatic steatosis as assessed by MR spectroscopy. The second trial was a controlled, open-label study that compared metformin 1.5 g/day plus lifestyle intervention to lifestyle intervention alone in 57 children with NAFLD [71]. After 24 months of treatment, children in both groups demonstrated equal but significant improvement in ALT and liver histology with decreased steatosis, ballooning and lobular inflammation. The mild nature of disease in both treatment groups, combined with the effectiveness of lifestyle intervention, precluded evaluation of a metformin effect.

Given the lack of randomized controlled clinical trials and the inclusion of subjects with minimal disease in some trials, there is insufficient evidence to support the use of pharmacological therapies in pediatric NAFLD. The Treatment of Nonalcoholic Fatty Liver Disease in Children (TONIC) trial conducted by the NIH-supported Nonalcoholic Steatohepatitis Clinical Research Network addresses the limitations of previous pediatric studies [72]. In this large, multicenter, randomized, placebo-controlled, double-blinded trial, 173 nondiabetic children with biopsy-proven NAFLD are receiving either vitamin E, metformin or placebo therapy for 96 weeks. Histological response to treatment is being assessed by an end-of-treatment liver biopsy. Results from this trial will be available in 2010.

Conclusion

Nonalcoholic fatty liver disease is the most common cause of chronic liver disease in children. Along with the rapid rise in childhood obesity, there has been an increase in the prevalence and recognition of pediatric NAFLD. Although the disease shares many similarities with NAFLD in adults, significant histological differences exist between adult and pediatric

NAFLD to warrant caution in extrapolation of adult data. Several recent studies have shed light on risk factors for pediatric NAFLD and the association between fatty liver, Type 2 diabetes and cardiovascular risk in children. A better understanding of the genetic and environmental factors that contribute to NAFLD prevalence and severity will enable improved clinical diagnosis and management of NAFLD patients and may identify new molecular targets for pharmacological treatments.

Future perspective

Given the continued rise in pediatric obesity, the prevalence and public health burden from NAFLD is likely to expand. Multiple genetic and environmental factors, including sex, race, diet and body habitus have been identified as risk factors for NAFLD and should inform future attempts to develop screening protocols. The current reliance on liver biopsy for diagnosis and staging, along with the lack of published guidelines for screening high-risk children, has contributed to the massive underevaluation and underdiagnosis of NAFLD. Given the high prevalence of NAFLD in children and the realistic potential for progression to cirrhosis, there is an urgent need for noninvasive diagnostic tools to identify children at risk for NASH. Several studies in the pediatric population have identified potential variables associated with more severe NAFLD that might serve as criteria in the selection of children who should undergo more extensive evaluation. Given our new understanding of the highly heritable nature of NAFLD, family members of children with NAFLD should be considered at high risk for NAFLD, even in the absence of obesity and elevated aminotransferases.

Although the natural history of pediatric NAFLD is not clear, early experience shows that the disease may progress to end-stage liver disease and is associated with significantly shorter survival. Recently, obese children with NAFLD were identified as having a more severe cardiovascular risk profile and a higher prevalence of atherosclerosis and diabetes than their age-, gender- and BMI-matched peers. Although it is unclear whether NAFLD confers additional risk beyond the traditional cardiovascular risk factors, children with NAFLD will likely be in a high-risk group for future cardiovascular events. Thus, the goals for treatment of fatty liver disease should focus on both the prevention of end-stage liver and cardiovascular disease. Currently, no consensus exists for the treatment of pediatric NAFLD or the prevention of cardiovascular disease in this population. Some therapies for the treatment of NAFLD have demonstrated promising results in preliminary pilot studies, but appropriately powered, randomized, double-blinded, placebo-controlled, multi-center studies are needed to support the use of such therapies and to establish their safety in pediatric NAFLD. The success of clinical trials assessing potential treatment paradigms will be highly dependent on the establishment of uniform diagnostic criteria and better noninvasive diagnostic and staging methods. Current evidence suggests that MRI, which can accurately quantify steatosis and fibrosis, may be useful in future clinical practice for diagnosis and longitudinal monitoring of NAFLD and evaluation of histological response to treatment.

Executive summary

Epidemiology

- More than 15% of children in North America, Great Britain, western Europe and Korea are obese.
- An autopsy study estimated the prevalence of nonalcoholic fatty liver disease (NAFLD) to be 9.6% in children and adolescents.
- The prevalence of NAFLD in obese adolescents is reportedly between 10 and 77%.

- NAFLD is more prevalent in boys and children of Asian, Hispanic and Native American descent.
- When adjusted for age, body mass index and gender, African–American children have the lowest prevalence of NAFLD.

Diagnosis

- Liver biopsy with histology is required for definitive diagnosis of NAFLD.
- In clinical practice, the diagnosis is usually suspected upon finding elevated serum aminotransferases or hepatomegaly on exam.
- NAFLD in children is underdiagnosed by primary care physicians and pediatric subspecialists.

Serum biomarkers & noninvasive screening

- Development of noninvasive methods is needed to identify children with NAFLD and predict those at increased risk for progression to nonalcoholic steatohepatitis (NASH).
- Increased serum aspartate aminotransferase, γ -glutamyl transpeptidase and positive antismooth muscle antibody titers are most consistently associated with pattern and severity of NAFLD and appear superior to alanine aminotransferase in distinguishing NAFLD pattern.
- The enhanced liver fibrosis (ELF) test may be able to accurately assess the level of fibrosis in pediatric NASH.

Imaging

- Accurate noninvasive imaging techniques to diagnose and monitor NAFLD are being developed.
- Ultrasound is limited by its unreliable ability to quantify steatosis or fibrosis.
- MRI, with certain modifications, enables rapid, reproducible measurements of steatosis and fibrosis.
- Owing to the ionizing radiation of computed tomography (CT) and because alternative modalities are available, CT should play no role in the clinical management or research of pediatric NAFLD.

Histopathology

- Two distinct subtypes of pediatric NAFLD have been identified and appear to be associated with different demographics.
- Type 2 NASH, defined by the presence of steatosis with portal inflammation and/or fibrosis in the absence of ballooning degeneration and perisinusoidal fibrosis, is a distinct pattern confined to children.
- Type 1 NASH, defined by steatosis with ballooning degeneration and/or perisinusoidal fibrosis in the absence of portal features, is consistent with the histological features described in adult NASH and appears to be less common than type 2 NASH in children.

Pathogenesis

- Both genetic and environmental factors are likely responsible for the development of NAFLD and its progression from simple steatosis to NASH.
- Obesity and insulin resistance appear to be essential factors.

- Recent studies suggest excess dietary fructose as a cause.
- A significant genetic component likely explains why some obese children develop NAFLD whereas others do not.
- A familial aggregation study in overweight children with and without NAFLD found that fatty liver is a highly heritable trait.
- Genome-wide transcriptional profiling analysis has identified several candidate predisposition genes.

NAFLD, the metabolic syndrome & cardiovascular risk

- Metabolic syndrome (MetS) is a clustering of risk factors associated with the development of cardiovascular disease and Type 2 diabetes mellitus.
- NAFLD poses a risk factor for the development of MetS in children.
- Fatty liver likely precedes the development of MetS and Type 2 diabetes mellitus.
- Serum protein fetuin A may link obesity, insulin resistance, MetS and NAFLD.
- NAFLD in the pediatric population is associated with carotid atherosclerosis and cardiovascular risk.

Treatment

- The generally accepted therapy for pediatric NAFLD includes lifestyle modification with improved diet and exercise.
- Weight loss following lifestyle intervention is associated with significant improvement in liver histology and serum aminotransferases in children with presumptive NAFLD.
- Several pilot studies assessing the use of metformin and antioxidants in the treatment of pediatric NAFLD demonstrate promise.
- An ongoing multicenter, randomized, placebo-controlled, double-blind trial (TONIC) compares the effectiveness of metformin versus vitamin E in the treatment of pediatric NAFLD as evidenced by improvement in liver histology.

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• of interest

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Figure 1. Photomicrographs of a pediatric liver biopsy

(A) Type 1 nonalcoholic steatohepatitis (NASH). Photomicrograph of a pediatric liver biopsy demonstrating macrovesicular steatosis, ballooning degeneration and perisinusoidal fibrosis, exemplifying a type 1 NASH pattern. **(B)** Type 2 NASH. Photomicrograph of a pediatric liver biopsy demonstrating macrovesicular steatosis without evidence of cellular injury or lobular inflammation, with mild periportal fibrosis and lack of perisinusoidal fibrosis. This pattern exemplifies a type 2 NASH often seen in children.

Figure 2. Proposed mechanisms for hepatic steatosis in nonalcoholic fatty liver disease

Several mechanisms potentially contribute to the development of fatty liver. (1) Visceral adipose accumulation is associated with adipokine dysregulation and increased delivery of FFAs directly into portal circulation. Oversecretion of leptin and TNF- α and hyposecretion of adiponectin contribute to peripheral insulin resistance. (2) Peripheral insulin resistance results in decreased glucose uptake by muscle and increased FFA liberation from adipose. The result is persistently elevated levels of circulating insulin, FFAs and glucose, which cause a series of changes in hepatic metabolism that ultimately lead to steatosis, (3) increased hepatic DLG from glucose, (4) increased synthesis of TGs from peripherally derived FFAs, (5) decreased hepatic β -oxidation and (6) impaired synthesis of ApoB with decreased export of TG as VLDL. DLG: *De novo* lipogenesis; FFA: Free fatty acid; Glc: Glucose; TG: Triglyceride.