Current Concepts in Pediatric Nonalcoholic Fatty Liver Disease

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KEYWORDS
- Steatohepatitis • NASH • Obesity • Metabolic syndrome • Histopathology

KEY POINTS
- Nonalcoholic fatty liver disease (NAFLD) manifests as a spectrum of disease (steatosis to steatohepatitis to cirrhosis) and its increasing prevalence is a direct result of rapidly rising obesity rates.
- Pediatric NAFLD may be distinctly different from that found in adults by histologic evaluation; however, the cause of these differences is unknown.
- The exact pathophysiology of NAFLD is largely unknown, but histologic findings provide insight into possible mechanisms and targets for therapy.
- Few effective therapies are successful in treating NAFLD, and lifestyle modification remains the first-line of therapy in children.
- Randomized, controlled trials demonstrate resolution of NASH with vitamin E therapy, which is the current recommended treatment in pediatrics by expert guidelines.

PEDIATRIC EPIDEMIOLOGY AND RISK FACTORS

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of liver disease in children and its increasing prevalence is associated with the concomitant rise in obesity. Features of the metabolic syndrome criteria are each associated with NAFLD, including obesity, insulin resistance, and hypertriglyceridemia, and children with the metabolic syndrome have 5 times the odds of having NAFLD as overweight and obese children without metabolic syndrome. Although the prevalence rates of pediatric obesity have remained stable over the past decade, estimates on the prevalence of NAFLD in pediatrics vary widely.

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The variability in prevalence estimates is in part owing to a relative lack of sensitive screening methods. Alanine transaminase (ALT) is a marker of hepatic injury and when combined with imaging that has sensitivity to fat infiltration, and when combined with other laboratory tests to eliminate other causes of fatty liver clinical suspicion, can be used to diagnose NAFLD. However, ALT is not sensitive, and normal cutoff values are based on adult values; appropriate cutoffs have not yet been defined in children, and are likely lower than current cutoffs, because “normal” ranges have shifted upward with the trend in higher body mass index \( z \)-scores.\(^3\) More work is needed to determine appropriate cutoffs in children, and to determine other more sensitive markers of disease.

Despite this challenge, attempts have been made to get accurate prevalence rates in children. The SCALE study conducted a retrospective review of 742 children from the San Diego, California area, between the ages of 2 and 19 years, who had an autopsy performed by a county medical examiner for reasons related to unnatural rapid death. In this study, 9.6% of all children and 38% of obese children were found to have NAFLD.\(^4\) In contrast, in a large European cohort of children, the prevalence of elevated ALT was 11% of the study population, and 17% in the extremely obese children.\(^5\) Finally, in an National Health and Nutrition Examination Survey cohort of children, 8% of the population had an elevated ALT.\(^6\) Across all 3 studies, however, older, male, Hispanic children were found to be at greatest risk.\(^4\)–\(^6\)

**NONALCOHOLIC FATTY LIVER DISEASE AS A SPECTRUM OF DISEASE**

NAFLD results from an accumulation of excess free fatty acids and triglycerides, demonstrated by hepatocellular macrovesicular steatosis.\(^7\) NAFLD is an all-encompassing term that refers to a spectrum of disease. Although nonalcoholic fatty liver refers to steatosis without inflammation or necrosis and is considered relatively benign, this condition may progress or present with inflammation, hepatocyte injury and cell death, called nonalcoholic steatohepatitis (NASH).\(^8\) NASH may be present with or without fibrosis, with potential progression to cirrhosis and increasing the risk of hepatocellular carcinoma.\(^9\)

**THE ROLE OF LIVER BIOPSY**

Liver biopsy is required for definitive diagnosis and staging of NAFLD owing to insufficiently validated or developed biomarkers or imaging techniques.\(^10\) For example, pediatric ultrasound imaging has shown good correlation with steatosis but not with fibrosis or liver injury.\(^11\) Liver biopsy is also required to rule out comorbid disease as cause of elevated ALT. Skelly and colleagues\(^12\) found that one-third of patients with suspected NAFLD were diagnosed with a condition other than NAFLD by biopsy, reinforcing the role of biopsy and the lack of specificity of ALT. Furthermore, biopsy is required for determination of nonprogressive (NAFL) versus progressive (NASH) disease.\(^8\)

Unfortunately, liver biopsy carries significant risks of morbidity and mortality, rendering it an unacceptable screening tool.\(^13\) Therefore, guidelines have been developed to help clinicians balance possible risk with the need for accurate diagnosis. The American Association for the Study of Liver Disease published guidelines in 2012 that recommend clinicians reserve liver biopsy for only subjects who will benefit and for children with unclear diagnosis or consideration for medication.\(^14\) Its European counterpart, the European for the Study of Liver Disease, released a position statement that acknowledged liver biopsy provides both diagnostic and prognostic information on fibrosis, and potential for progression if fibrosis is suspected by noninvasive methods. No specific pediatric recommendations were made.\(^15\)
PEDIATRIC DISEASE PROGRESSION

Although biopsy is desirable for the evaluation of fibrosis, only a minority of children will progress to it. Published data on the natural history in children is minimal. In a single retrospective longitudinal study, 66 children with NAFLD were followed for 20 years. In this group, 2 children died and 2 underwent liver transplantation owing to decompensated cirrhosis. Of 5 children with diagnostic biopsy at the start of the study, 2 developed fibrosis and 2 developed fibrosis with cirrhosis. Most of the other literature available is adult focused. In adult studies, one-third of patients with NASH progress to cirrhosis, and NASH was identified as the leading risk factor for hepatocellular carcinoma. Hepatocellular carcinoma is very rarely seen in children with NASH; however, those patients who acquire NAFLD earlier in life are likely have increased vulnerability to further liver disease in the future, and longer exposure to disease-related provocation.

HISTOLOGIC FEATURES OF PEDIATRIC FATTY LIVER DISEASE

Liver biopsies for NAFLD demonstrate a wide range of histologic findings. Simple steatosis, or nonalcoholic fatty liver, has the same threshold in children and adults, which is lipid accumulation evident in greater than 5% of hepatocytes. Steatosis must be primarily macrovesicular, indicating there is a single large fat droplet with or without multiple smaller intracytoplasmic droplets, accompanied by nuclear displacement to the cellular periphery (Fig. 1A). A smaller proportion of patients

Fig. 1. Fatty liver (steatosis). (A) Macrovesicular steatosis. This example of moderate large droplet steatosis, the hepatocyte nuclei are pushed to the periphery of the cell by large vacuoles of triglyceride (yellow arrow). (B) Microvesicular steatosis. The majority of lipid vacuoles in this case are small (yellow arrows), with the hepatocyte nuclei remaining central in the hepatocyte cytoplasm. Note that in some hepatocytes the small vacuoles are coalescing into large droplets (black arrows). (Hematoxylin and eosin stain; original magnification: A, ×200, B, ×400).
may have a mix of small and large droplet accumulation. There is an even smaller subset of patients who may have microvesicular steatosis, where there are many tiny lipid droplets with preservation of a centrally located nucleus (Fig. 1B). In adults, steatosis severity is positively associated with a progression to NASH. Chalasani and colleagues found that levels of steatosis severity positively correlated with lobular inflammation, zone 3 fibrosis, and definite steatohepatitis.

Although steatosis is consistent between adults and children, steatohepatitis often differs significantly. Children can have the same features as adult-type NASH (type 1), but a subset of children have different histologic features known as type 2 NASH. These children are younger, male, Asian, Hispanic, and Native American. Pediatric NASH may also have features of both types. In a study of 100 pediatric patients with NAFLD, Schwimmer and colleagues found type 1 (adult type) NASH in 17% of subjects, and type 2 (pediatric type) NASH in 51%. It has been proposed that the switch from pediatric to adult type NASH, which is more common in older children, is related to the hormonal changes of puberty or possibly to nutritional factors.

Type 1 NASH is defined by a set of minimal criteria. These criteria include steatosis, hepatocellular ballooning, and perivenular (zone 3) lobular inflammation (Figs. 2 and 3). Hepatocellular ballooning is marked by enlarged hepatocytes with rarefied...

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**Fig. 2.** Nonalcoholic steatohepatitis (NASH) type 1. Type 1 NASH is the most common pattern seen in adults and at its onset involves centrilobular regions (acinar zones 3). (A) At low magnification there is centrilobular (c) large droplet fat, hepatocyte ballooning, and inflammation (the minimal criteria for NASH). Note that the portal tract (PT) is also mildly inflamed. (B) Centrilobular steatosis, balloononed hepatocytes and inflammation are evident. (C) The typical “chicken-wire” perisinusoidal and pericellular pattern of fibrosis is evident on this trichrome stain (A, stain: hematoxylin and eosin stain; original magnification, ×100; B, ×400; C, stain: Masson trichrome; original magnification, ×200).
reticular cytoplasm indicating cell injuries that are the result of alterations in intermediate filament cytoskeleton. Owing to this change, loss of keratin 8/18 immunostaining may serve as marker for recognition of hepatocyte ballooning. Apoptotic bodies and lytic necrosis also may be present. Lobular inflammation in type 1 NASH is, by definition, in zone 3 or perivenular. This lobular inflammation seen in type 1 NASH is often mild with a mixed inflammatory cell infiltrate. Polymorphs sometimes surround ballooned hepatocytes (which usually also show intracytoplasmic Mallory-Denk bodies), a phenomenon referred to as “satellitosis” (Fig. 4). Scattered lobular microgranulomas and lipogranulomas are common. It is possible to have mild chronic lobular and portal lymphocytic inflammation that can indicate resolution in treated NAFLD. It should be noted that fibrosis is not required for the diagnosis of steatohepatitis but, when present, is usually perisinusoidal (Fig. 2C; Table 1). In contrast, however, borderline zone 1 or type 2 NASH is quite different histologically, and is more common than type 1 in children, and relatively unique to the pediatric population. The distinctive features of type 2, or pediatric type NASH, are portal-based (zone 1) chronic inflammation and fibrosis, moderate to severe steatosis, and absence of zone 3 lesions (Figs. 5 and 6). It is less common to find hepatocellular ballooning, or Mallory-Denk bodies (see Fig. 3B), as found in type 1.

Fig. 3. Type 1 nonalcoholic steatohepatitis (NASH). (A) The hepatocytes in the centrilobular region show ballooning and considerable nearby inflammation. Mallory-Denk bodies are present in several ballooned hepatocytes (yellow arrows) (seen to better advantage in B). (B) At the upper right, several ballooned hepatocytes with wispy, rarefied cytoplasm contain Mallory-Denk bodies (yellow arrows). The blue arrow indicates the hepatocyte nucleus. The surrounding inflammatory infiltrate is mixed, predominantly lymphocytes with a few neutrophils (A, stain: hematoxylin and eosin; original magnification, ×200; B, ×400). CV, central vein.
Finally, both types 1 and 2 can progress to fibrosis. Noncirrhotic, NASH-related fibrosis has a characteristic perisinusoidal and pericellular (chicken wire) pattern in zone 3, but generally shows portal tract predominance in type 2 NASH. This fibrosis is associated frequently with active lesions of NASH, but also may be seen in their absence, possibly indicating prior episodes of steatohepatitis. In the progression of NASH, portal and periportal fibrosis may be observed leading to bridging fibrosis. Although steatosis is the first step in the progression of NAFLD, in advanced fibrosis and cirrhosis, steatosis can be absent (Fig. 7). Once NASH has become true cirrhosis, it is most commonly macronodular or mixed.

### SYSTEMS PROPOSED FOR HISTOLOGIC EVALUATION

Because NAFLD is a spectrum of disease from steatosis to cirrhosis, and histologic appearance has direct implications for prognosis, attempts have been made to standardize histologic evaluation of NAFLD liver biopsies. Two main scoring systems have been used, the NAFLD Activity Score and the Brunt scoring system.

The NAFLD Activity Score was developed by the NASH Clinical Research Network and was designed as a quantitative tool for evaluation of NASH. This score uses degree of steatosis, lobular inflammation, and ballooning with a separate grade for fibrosis. The Brunt scoring system is a semiquantitative assessment by using

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**Table 1**

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<td>Mallory-Denk bodies</td>
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<td>Fibrosis</td>
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Fig. 5. Type 2 nonalcoholic steatohepatitis (NASH). This common pediatric type of NASH is centered on the portal tracts (PT), which show chronic inflammation and periportal fibrosis reminiscent of chronic hepatitis. The centrilobular hepatocyte ballooning and inflammation are absent. *Inset,* A central vein (CV) is shown, further emphasizing the absence of hepatocyte ballooning and inflammation from this region (stain: hematoxylin and eosin; original magnification, ×100; inset: stain: hematoxylin and eosin; original magnification, ×200).

Fig. 6. Type 2 nonalcoholic steatohepatitis (NASH). (A) The portal tracts in type 2 NASH show chronic inflammation, sometimes with periportal interface hepatitis (*yellow arrow* at bottom). Note the predilection for large droplet fat in pediatric liver biopsies to accumulate in periportal regions. (B) Trichrome stain demonstrates irregular periportal fibrosis (*A,* stain: hematoxylin and eosin; original magnification, ×100; *B,* stain: Masson trichrome; original magnification, ×40).
mild, moderate, or severe designations in macrovesicular steatosis, ballooning, and lobular and portal inflammation.  

HISTOLOGIC INSIGHTS INTO PATHOGENESIS

The histology of NAFLD is well-described; however, the pathophysiology is not as well-understood. It was initially proposed that NAFLD was the result of 2 “hits.” In this model, the first hit is the accumulation of fat in hepatocytes, which is caused by caloric excess and subsequent development of insulin resistance and hyperinsulinemia. In this model, steatosis is the histopathologic manifestation of first hit, which occurs owing to an imbalance between fatty acid uptake and catabolism in liver. Peripheral tissue lipolysis, de novo lipogenesis, and dietary intake of fatty acids produce an overall influx of lipid into hepatocytes and a decrease in fatty acid oxidation, and secretion of free fatty acids as very low-density lipoproteins results in a retention of hepatic lipid. This imbalance produces a net increase in hepatocyte lipid content. Histology supports this with severity of steatosis seen in nonalcoholic fatty liver. The next hit may be multifactorial. One proposed insult includes increased reactive oxygen species (ROS), which promote hepatocellular damage, perhaps through peroxidation or epoxidation of lipids. Histopathologic findings support this theory with the presence of megamitochondria and microvesicular steatosis. Megamitochondria are a known consequence of ROS accumulation, as a result of mitochondrial membrane fusion. This may decrease oxygen consumption to decrease ROS levels. If ROS decreases, the mitochondria return to normal size and function; however, continuous exposure of cells containing megamitochondria to additional free radicals induces apoptosis. Furthermore, microvesicular steatosis is caused by oxidized phospholipid on surface of small lipid droplets within hepatocytes. Oxidized phospholipid is formed nonenzymatically by ROS, and products of oxidative damage are often found in zone 3, indicating the potential role of ROS in the pathophysiology of NAFLD. Overexpression of cytochrome P450 2E1 (CYP2E1) has been found in zone 3 in patients with NASH and insulin resistance. CYP2E1 is known to generate ROS.
Glutathione depletion has also been implicated in the development of NASH, owing to its role in recovery from ROS-related stress. Glutathione is a major intracellular antioxidant in the liver and because oxidative stress and lipid peroxidation may contribute to the pathogenesis of NASH, and its depletion may predispose obese individuals to the development of hepatocellular injury in NASH.40,41 Patients with NASH may have a diet deficient in antioxidant-rich foods. Rodent models of glutathione deficiency have supported this finding,42 and supplementing with glutathione-enhancing agents have shown some protection against NASH-related liver injury.18,44

There is evidence that other hepatocellular metabolic processes are affected. Liver biopsies of patients with NASH exhibit ballooning degeneration and Mallory-Denk bodies, which are ubiquinated (or other protein-bound) intermediate filament proteins.26 Cellular processes that contribute to Mallory-Denk body formation include chronic stress, stress-induced protein misfolding (promoting endoplasmic reticulum stress), proteasome overload, transamidation of cytokeratin K8, and autophagy. Mallory-Denk bodies, therefore, act as a histologic and potential prognostic marker of NASH.45

The progression of disease and development of fibrosis also provides histologic clues to pathogenesis. In 2 separate studies, stellate cell activation was evaluated by immunohistochemistry, and found zone 3 accentuation in human liver biopsies of NASH.46,47 In humans, fibrosis is also associated with hepatocyte progenitor cell (oval cell) accumulation, and NAFLD is no exception. These cells inhibit mature hepatocyte replication, which results in expansion of the hepatic progenitor cell (oval cell) population. It is thought that the increased number of these immature hepatocytes is, in part, responsible for the increased risk of hepatocellular carcinoma.48

The cause of these metabolic derangements and the reason for such varied severity in patients with NAFLD is largely debated. Adipokines have been proposed to have a causal role in the development and progression of disease. Low levels of adiponectin and high levels of leptin in combination have a strong independent association with presumed early stage NASH,49 and adipokine expression has been associated with regulation of hepatic lipid receptors in obese patients with NAFLD.50 Twin, familial, and epidemiologic studies have suggested a genetic component to NAFLD51–53 and genome-wide association studies have identified variants in patatin-like phospholipase domain containing 3 and transmembrane 6 superfamily member 2 genes in NAFLD.54,55 As with many other inflammatory diseases, the microbiome has also been implicated. There have been a number of recent studies on the intestinal microbiome of obese and NAFLD patients with varying results, but when controlled for exposure to medication known to alter the microbiome, an increase in Bacteroides/Firmicutes ratio was found in children who were obese and had NASH compared with lean healthy controls.56

Finally, it should be noted that the reason for the different patterns of NAFLD between adults and some children remains unexplained, and it is unclear if these differences are owing to truly different pathogenesis, different phenotypes of a similar pathogenesis, or natural disease progression with age. The recent randomized, placebo-controlled, double-blind trial of delayed release cysteamine as a treatment for NASH, demonstrated that there are significant differences in histology (in post hoc analyses) for children who were younger, less obese, and had “type 2” NASH. This is of importance because it may indicate that the etiopathogenesis is in fact different, and thus natural history and response to treatment may be different.44 This study serves as a possible example, although further drug and mechanistic studies are needed to confirm this observation.
TREATMENT AND MANAGEMENT

Treatment of NAFLD is directed at a reduction in hepatocyte injury and the prevention of fibrosis. The mainstay of treatment in pediatrics remains lifestyle modification and diet modification. There are several pediatric studies that have shown biochemical and biopsy-proven improvements after these types of interventions. These interventions have included a hypocaloric diet and daily exercise. Marchesini and colleagues found that a 7% to 10% decrease in body weight was necessary for improvement in steatosis and NASH remission.

Because the microbiome has been implicated in the pathogenesis of NAFLD, probiotics as a treatment for this disease have also been studied. Obesity has been shown to alter the gut microbiota, which communicates with the liver via the portal system. Thus, it is thought that, by shifting the microbiome back toward that of a lean person with probiotic therapy, the metabolic effects of the abnormal microbiome on the liver can be reversed. Probiotics are generally considered safe and well-tolerated; however, trials in NAFLD are limited. In 1 small study, obese children were treated with *Lactobacillus rhamnosus* for 8 weeks, resulting in a reduction in ALT. In obese pediatric subjects with NAFLD, those put on probiotic VSL #3 showed evidence of improved steatosis, decreased body mass index, and increased circulating glucagon-like peptide. Studies remain limited, but there is a modicum of evidence that probiotics and synbiotics improve some components of NAFLD and the metabolic syndrome.

Long chain omega-3 fatty acids have also been studied as potential therapy for NAFLD in children. In a Western diet, typically many more omega-6 fatty acids are consumed than omega-3 fatty acids. This change in ratio of omega-6 to omega-3 is thought to increase proinflammatory metabolites. Supplementing with additional omega-3 fatty acids would restore the ratio and decrease production of these metabolites. In a pediatric cohort of 60 patients with biopsy-proven NAFLD, DHA supplementation was associated with improvement in steatosis as well as decreased ALT and triglyceride levels. More recent studies in children and adults have not been able to replicate the study, so DHA is not used as a therapy.

Elevated oxidative stress is recognized as a contributor to NAFLD severity, so antioxidant augmentation has been tested as a potential therapy. Lavine and colleagues showed a normalization of aminotransferases and alkaline phosphatase in children with NASH on oral vitamin E in a pilot study. In the multicenter, randomized, placebo-controlled, double-blind TONIC trial, it was found that there was significant resolution of NASH on vitamin E (800 IU orally per day for 96 weeks) relative to placebo (P = .006), and significant improvement in the NAFLD Activity Score. Metformin, an insulin sensitizer, was also assessed in the TONIC trial (1 g/d), but did not result in improved histology.

Bariatric surgery has been recommended for severely obese adolescents and obese adolescents with major comorbidities. Various bariatric surgeries decrease steatosis and improve inflammation and fibrosis in patients with NASH.

EMERGING THERAPEUTIC TARGETS AND THERAPIES

As new insights are gained with regard to the pathophysiology, new treatment targets become available. Pentoxifylline is a phosphodiesterase inhibitor that antagonizes the proinflammatory cytokine tumor necrosis factor-α. Studies demonstrate improvement in aminotransferases, steatosis, inflammation and fibrosis in adult subjects treated with this drug.
Farnesoid X receptor is a bile acid receptor that mediates lipid and glucose homeostasis. In a multicenter, randomized, placebo-controlled trial, the farnesoid X receptor agonist obeticholic acid significantly improved multiple histologic features of NASH, including fibrosis. This drug is now in being tested in a Food and Drug Administration phase III trial.

Most recently, a multicenter, randomized, double-blind trial of delayed release cysteamine for treatment of NAFLD in children has shed light on pathogenesis and new treatment modalities. Cysteamine is a small molecule that reacts with extracellular cystine to form cysteine, which is then taken up into cells and used to support glutathione synthesis. ALT reduction by cysteamine in the treatment group was improved significantly compared with placebo, but the primary histology endpoint, reduction in the NAFLD Activity Score by 2 or more points without worsening of fibrosis, did not show significant improvement. A post hoc analysis reveals there was histologic improvement in those who were younger, less heavy, and with type 2 NASH. This demonstrates that surrogate endpoints for clinical trials may not always accurately reflect recognized histologic ones, particularly in children. This study highlights that the etiopathogenesis may be different between pediatric-type and adult-type NASH; therefore, response to treatment may be different. This calls for recognition of the need for appropriate histology-based endpoints for therapeutic trials in pediatrics.

SUMMARY

NAFLD is a spectrum of disease from steatosis to steatohepatitis to fibrosis and cirrhosis and its increasing prevalence is a direct result of historically high rates of obesity. Some children with NAFLD demonstrate distinct histopathologic differences from the pattern found in adults; however, the cause of these differences is unknown. Hepatocyte lipid accumulation is the first step in a cascade of metabolic events that are thought to cause NAFLD, and histologic findings provide insight into these events. There are few well-studied, effective therapies that are successful in treating NAFLD, and lifestyle modification remains the primary therapy in children. Administration of vitamin E in children with NASH has shown to result in significant resolution relative to placebo, and guidelines set forth by the American Gastroenterological Association, American Association for the Study of Liver Disease, and the American College of Gastroenterology recommend vitamin E treatment for children with biopsy-proven NASH. Trials of novel drugs are in multiple phase trials of adults with NASH, and as efficacy and safety are established, these therapies may be tenable for use in children. However, biopsy-driven histology endpoints will be necessary to establish whether future therapies can improve either pediatric or adult-type NASH in children.

REFERENCES


