

Pediatric Nonalcoholic Fatty Liver Disease in 2009

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Within the so-called “globesity” epidemic, the International Obesity Task Force estimated that there are at least 155 million persons who are overweight/obese, including 30 to 45 million obese children worldwide.¹⁻⁴ In parallel with epidemic obesity, nonalcoholic fatty liver disease (NAFLD) has also been increasingly recognized worldwide in the last decade. At present, NAFLD is identified as an important liver disease in children, occurring even in the very young.⁵ The incidence in the general population is 2.6% but increases to 53% in obese children; thus, NAFLD is expected to become the most common cause of pediatric chronic liver disease in the near future.⁶

NAFLD includes a broad spectrum of liver abnormalities, ranging from accumulation of fat (simple steatosis) to non-alcoholic steatohepatitis (NASH), with varying degrees of inflammation and fibrosis, progressing to cryptogenic cirrhosis.⁷ Simple steatosis has a favorable clinical outcome, whereas NASH is progressive and more difficult to treat effectively. The presence of inflammation, ballooning degeneration, Mallory bodies, necro-inflammation, and pericellular fibrosis characterizing NASH can all lead to cirrhosis.^{8,9}

The common link between obesity and NAFLD is increased insulin resistance (IR). As with all the metabolic abnormalities that cluster into the metabolic syndrome, visceral obesity correlates with severe insulin resistance and fatty liver.⁹⁻¹²

There is wide and growing recognition of NAFLD, but no significant advances have been achieved in its diagnosis and treatment. The sense of urgency in developing diagnostics is linked to the epidemiology of pediatric disease but also to the increased risk of developing cirrhosis and hepatocellular carcinoma in adulthood.¹³⁻¹⁶

We offer a concise overview of recently published advances and the authors’ perspective on the risk factors, diagnostic paradigm, prevention, and treatment of pediatric NAFLD.

Risk Factors

The development of NAFLD in children requires the coexistence of multiple factors. Among the numerous risk factors,

ALT	Alanine aminotransferases
BMI	Body mass index
CATCH	Child and Adolescent Trial for Cardiovascular Health
CT	Computerized tomography
ELF	Enhanced Liver Fibrosis
HDL	High-density lipoprotein
IR	Insulin resistance
MRI	Magnetic resonance imaging
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
NHANES	National Health and Nutrition Examination Survey

many are similar to risk factors that have been identified in the adult population, including obesity, visceral adiposity, insulin resistance, and presence of other features of the metabolic syndrome. Other risk factors, such as race/ethnicity, sex, and distribution and progression of pubertal development, are exclusive to pediatric NAFLD.⁹

Overweight and obesity are consistently identified as significant risk factors for NAFLD in studies from North America, Europe, and Asia.^{5,9,10} Approximately 25% of children referred to obesity centers have elevated serum alanine aminotransferase (ALT) levels.^{17,18} Data from the *National Health and Nutrition Examination Survey* (NHANES) reported that 6% of overweight adolescents and 10% of obese adolescents had elevated ALT levels.¹⁹ Data from The Child and Adolescent Trial for Cardiovascular Health (CATCH) indicated that a multivariate model significantly predicted the serum ALT level using the combination of sex, race/ethnicity, and BMI and accounted for 36% of the individual variance.²⁰

Abdominal obesity, strongly associated with visceral adiposity, is more powerful than BMI in predicting NAFLD^{21,22} and contributes to liver fibrosis in children with NAFLD.²³⁻²⁶

Insulin resistance is thought to be a critical factor in the pathogenesis of fatty liver and NASH in children.^{2,27}

Other components of the metabolic syndrome in adults have been assessed in children including hypertriglyceridemia, hypertension, and low level of high-density lipoprotein (HDL) cholesterol.²⁸ Hypertriglyceridemia has been found to be associated with hepatic steatosis in several series of children, and 1 study reported significantly lower HDL cholesterol levels in obese adolescents with suspected NAFLD compared with obese controls.^{29,30}

The adipocytokines leptin and adiponectin modulate insulin resistance and have been implicated in the progression of NAFLD. Increased serum levels of leptin and decreased levels of adiponectin, strongly associated with insulin resistance regulation, have been found in children with NAFLD.^{31,32}

Although genetic factors predisposing to NAFLD remain unknown, children from certain ethnicities (ie, Hispanics, Asians, and indigenous Americans) are more predisposed.³³ The basis for the racial/ethnic disparity in NAFLD prevalence is not determined but may be related to differences in body composition, insulin sensitivity, adipocytokine profile, or

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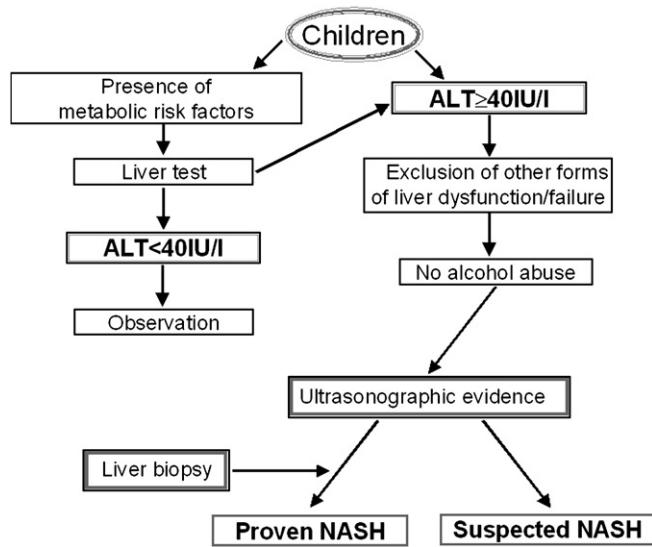


Figure. Diagnostic flow-chart.

other unidentified genetic and environmental factors.³⁴⁻³⁷ Interestingly, African-American children have a lower prevalence of NAFLD despite having increased risk factors for fatty liver such as obesity and insulin resistance.³⁸

Several case series and population-based studies suggest that NAFLD is more common in boys than in girls and that histological features of the disease may depend on sex.³⁹⁻⁴² Although sex has not been considered to be a risk factor for NASH in children, a male predominance of hepatic steatosis has been demonstrated.⁴³ Considering the hormonocentric view of NAFLD, these differences could be related to the levels of circulating sex hormones (estrogen-testosterone ratio), hepatic expression of sex hormone receptors, and pattern of growth hormone secretion.⁴⁴

Some studies suggest that age or, more specifically, pubertal stage, is a significant variable in the onset of NAFLD, and sex hormones and insulin resistance at puberty might explain this effect.⁴⁵⁻⁴⁷ There is also a subgroup of children who present with NAFLD at a younger age.⁴⁸

The importance of age, sex, and ethnicity as factors that determine the susceptibility to NAFLD among obese and/or insulin-resistant children requires further study.

Current Diagnostic Approaches

Diagnosis of NAFLD, as based on clinical, laboratory, and ultrasound evidence data, can be considered only presumptive. Children with NAFLD are often asymptomatic, and fatty liver is found incidentally by ultrasonography. Currently, diagnosis of NAFLD is based on blood tests (ie, ALT elevation) and ultrasound evidence of a fatty liver.^{42,43} However, although the elevation of ALT is a predictor of the presence of NAFLD, the serum levels of these hepatic enzymes in patients with NAFLD range from slightly over the upper limit of normal to 10 times more.^{49,50}

Table. Validated non invasive serum biomarkers of hepatic fibrosis in patients with NAFLD

Test name	Components	References
BARD score	BMI > 28 kg/m ² AST/ALT ratio > 0.8, diabetes	64
NAFLD score	Age, glucose, BMI, platelets, albumin, AST/ALT ratio	65
FibroMeter	Age, glucose, AST, ALT, ferritin, platelets, weight	66
Fibrotest/FibroSure	Age, sex, haptoglobin, A2 M, apo-A1, GGT, total bilirubin.	68
ELF	HA, TIMP-1, PIII-NP	67

BMI, Body mass index; AST, aspartate aminotransferases; ALT, alanine aminotransferases; A2 M, α_2 -macroglobulin; apo-A1, apolipoprotein A1; GGT, γ -glutamyl-transpeptidase; ELF, enhanced liver fibrosis; HA, hyaluronic acid; TIMP-1, tissue inhibitor of metalloproteinase-1; PIII-NP, N-terminal peptide of procollagen III.

NAFLD is indicated by the ultrasound presence of fatty infiltration of the liver, defined as exceeding 5% of hepatocytes. In adults, ultrasound has a sensitivity of 60% to 94% and a specificity of 73% to 93% for the diagnosis of liver fat, whereas the accuracy of ultrasound in children has not been established.⁵¹

The presence of metabolic risk factors from the metabolic syndrome must be considered as suggestive elements of disease.⁵² We depict the diagnostic flow chart adopted at our liver unit on the basis of recent reports (Figure).^{52,53}

Because of the limitations in clinical and laboratory tests and ultrasound, liver biopsy remains the gold standard for the definitive diagnosis. A liver biopsy may allow evaluation of the progression of NAFLD to NASH. Unfortunately, liver biopsy is an invasive technique that carries risk of complications, high cost, and a certain unreliability due mainly to sampling error. Sampling error, which is due to the small fraction of examined liver parenchyma, may cause relevant differences in the interpretations of liver biopsies.⁵⁴ Noninvasive methods to diagnose NASH are needed to reduce the reliance on liver biopsy and to obtain genuine prevalence data.

Perspective in Diagnosis

Noninvasive techniques currently in use to detect fatty liver include ultrasonography, computerized tomography (CT) scan, and magnetic resonance imaging (MRI).

Concerns regarding the use of CT in pediatric settings are raised because of the use of ionizing radiation and the availability of alternative modalities.⁵⁵ MRI appears to be a more accurate and reproducible technique in children.⁵⁵ Some interesting applications of MRI include the use of this technique to determine the correlation between hepatic steatosis and body adipose tissue distribution. It has been reported that because MRI is not subject to interpretation or inter-observer variation, it may be better than ultrasound for quantifying hepatic fat in children.⁵⁶⁻⁵⁸ However both CT and MRI do not allow staging of fibrosis. In our series of children with biopsy-proven NAFLD (n = 197), 58% had initial and 9% mild-to-severe fibrosis.²³

Alternative means of diagnosing fibrosis include transient elastography and a combination of serum markers. Transient

elastography by FibroScan (Echosens, Paris, France) has a high detection accuracy in both adults and children for more severe fibrosis.⁵⁹⁻⁶¹ Obesity may limit the accuracy of the technique. A number of serum biomarkers (Table), including those of the Enhanced Liver Fibrosis (ELF) Panel, have been tested as markers of fibrosis in adult and pediatric patients with NAFLD.⁶²⁻⁶⁷ Among them, we have recently demonstrated that ELF markers can predict liver fibrosis in children with NAFLD.⁶⁷ The diagnostic value of this panel could, in the future, be integrated with other circulating biomarkers (ie, pro-/anti-apoptotic proteins) identified by proteomic analysis.⁶⁸

Prevention and Therapy

Currently, there are no evidenced-based guidelines for how to treat NAFLD in children. Because obesity and overweight increase the risk for the progression of fatty liver and NASH, health care professionals encourage lifestyle changes (diet and proper exercise) as the first-step to prevention of the onset of NAFLD. A small but significant improvement in the BMI can normalize levels of ALT, reduce fatty liver infiltration, and necro-inflammation in children, whereas no change has been demonstrated in degree of fibrosis.^{69,70} A low-glycemic index diet may be effective.^{71,72} A rapid and excessive caloric restriction and weight loss may be dangerous because it might exacerbate metabolic disorders and promote hepatic portal inflammation, fibrosis, and focal necrosis.^{73,74} Despite the scarcity of data in children, optimization of a healthy diet in conjunction with exercise should be attempted in all children diagnosed with NAFLD.

Obesity surgery in adults can lead to improvement in NAFLD. Current evidence suggests that bariatric surgery may be an option also for extremely obese adolescents; appropriate selection criteria must be met.^{75,76}

There are pharmacological therapies that have been found to be effective in pilot studies; however, no conclusive results support the use of pharmacological agents in pediatric NAFLD because of the limited data on natural history of this disease in children. In addition, the interpretation of most studies is complicated by the use of different diagnostic methods.

The use of antioxidants, such as vitamin E, has been shown to improve ALT levels and liver histology in adult NAFLD.⁷⁷ One open-label study demonstrated that 2- to 4-month treatment with vitamin E normalized ALT, although continuation of treatment was necessary to sustain the effect.⁷⁸ On the other hand, 2 other studies demonstrated that only diet and physical exercise in children with NAFLD appear to lead to a significant improvement of liver function and glucose metabolism beyond any antioxidant therapy.^{79,80}

Ursodeoxycholic acid (UDCA), a cytoprotective agent, is able to reduce levels of ALT and improve liver histology in adult with NAFLD.⁸¹ In a randomized control trial, UDCA (10 to 12.5 mg kg d) was ineffective, both alone and when combined with diet, in reducing serum aminotransferase levels or the appearance of steatosis in 31 obese children.⁸²

As already described, insulin resistance is present in a majority of children and adolescents with biopsy-proven NAFLD. Thus, another approach to decreasing hepatic injury through reduction in steatosis is treatment with insulin-sensitizing agents. Metformin is a biguanide, which improves hepatic steatosis and hepatomegaly. The safety and efficacy of metformin have been established in the treatment of type 2 diabetes in the pediatric population.^{83,84} Administration of metformin was associated with a significant improvement in ALT and hepatic steatosis.⁸⁵⁻⁸⁷ Thiazolidinediones, such as pioglitazone and rosiglitazone, have been used successfully, improving insulin resistance and liver histology in adults.⁸⁸⁻⁹¹ Because minimal safety data are available on thiazolidinedione treatment of children with type 2 diabetes and none in children with NAFLD, the use of this class of drugs in pediatric patients must be studied.

Studies conducted in animals and pilot studies in adults have tested the use of several agents, including (1) lipid-lowering agents, such as fibrates, statins, and polyunsaturated fatty acids; (2) antioxidants and anti-inflammatory molecules, such as β -carotene, *N*-acetylcysteine, *S*-adenosyl-L-methionine, taurine, and betaine; (3) antibiotics and probiotics; and (4) drugs acting on signaling molecules, such as rapamycin.⁹²⁻⁹⁶ Two pilot studies are on-going in children to investigate the efficacy of novel agents (<http://clinicaltrials.gov>): (1) oral acarbose, an α -glucosidase inhibitor, is administered to evaluate safety of use and changes in intrahepatic fat content after 12-week administration; and (2) the effect of cysteamine, a known antioxidant and anti-inflammatory agent, being assessed based on biologic markers of steatohepatitis (ie, ALT serum levels).

Summary

Over the last decade, there has been a growing recognition of NAFLD as pediatric disease. In view of the lack of longitudinal studies describing the natural history of the disease and, particularly, poor diagnostic means of distinguishing benign from progressive forms, it is important to prevent fatty liver in children and attempt to intervene as soon as it is suspected.

Promoting physical activity and healthy eating early in the lives of children may decrease the risk of NAFLD. In the early preschool years, parents should be educated to include healthy food choices and active play into the lifestyles of their entire families.

Obese children presenting with concurrent metabolic abnormalities merit at the very least an assay of liver enzyme and ultrasound evaluation for fatty liver. Monitoring of liver histology can be worthwhile in extremely obese children with severely impaired metabolism, because they may develop fibrosis and hepatic insufficiency as young adults. ■

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