Nonalcoholic fatty liver disease in children

Nonalcoholic fatty liver disease (NAFLD) is probably the most common form of chronic liver disease in children in the USA and may continue to rise with the increasing prevalence of childhood obesity and metabolic syndrome. Although the exact pathophysiology of NAFLD is not well understood, insulin resistance, oxidative stress and the release of proinflammatory cytokines are suggested factors in the cascade of reactions resulting in NAFLD. The best diagnostic workup and treatment for NAFLD and nonalcoholic steatohepatitis are still being debated; however, early intervention to halt further progression and/or to reverse the disease process is recommended. Further studies are needed to better understand the demographics, pathogenesis, treatment, natural history and long-term prognosis of pediatric NAFLD. This review discusses current concepts regarding these issues in pediatric patients with NAFLD.

KEYWORDS: metabolic syndrome, NAFLD, NASH, obesity, pediatric

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Nonalcoholic fatty liver disease (NAFLD) is a chronic liver disease related to excessive accumulation of fat in the liver. NAFLD is a spectrum of liver diseases including simple steatosis, which represents fat accumulation without inflammatory changes, to the more sinister nonalcoholic steatohepatitis (NASH) detected on histology. Despite the fact that most patients are diagnosed as a consequence of unexplained altered liver function tests, the presence of NASH could be observed even with normal laboratory values [1–3]. NASH is a progressive liver disorder associated with elevated aminotransferase levels and a histological picture similar to alcoholic hepatitis in the absence of alcohol abuse. It can be associated with hepatomegaly and increased risk of 'cryptogenic' cirrhosis. The latter may progress to end-stage liver disease and cancer, as shown in adults [4]. The diagnosis of NAFLD is increasing in the pediatric population in direct proportion to an increase in childhood obesity [5]. Pediatric NAFLD must be considered a clinicopathological diagnosis requiring direct demonstration of liver steatosis and exclusion of other causes of fatty liver and/or hepatitis [6].

Epidemiology of NASH & NAFLD

NASH is believed to be the most common cause of abnormal liver chemistries in the USA [7,8]. Although a common cause of liver disease in children, the epidemiologic data of pediatric fatty liver are limited to single-center case series [3]. While obesity and insulin resistance are well-established risk factors for NAFLD, the role of gender, race and ethnicity on the prevalence of fatty liver disease in obese children is currently being explored. In a national, school-based sample of obese adolescents without known causes of chronic liver disease, boys were six-times more likely than girls to have an unexplained elevated alanine aminotransferase (ALT) [9]. In this school-aged population-based study, Hispanic adolescent boys had a higher prevalence of NAFLD than other demographic and ethnic groups. In a population-based study, Schwimmer and colleagues evaluated the prevalence of fatty liver in children by retrospective review of autopsies on children in San Diego County over a 10-year period. The overall prevalence of fatty liver in the general pediatric population was 13%. Fatty liver prevalence increases with age, ranging from 0.7% for ages 2–4 up to 17.3% for ages 15–19 years. Fatty liver prevalence differs significantly by race and ethnicity (Black: 1.5%; White: 8.6%; Asian: 10.2%; and Hispanic: 11.8%). The highest rate of fatty liver was seen in obese children in this study (38%) [10].

Pathogenesis of NAFLD

The pathogenesis of NAFLD is still poorly understood, with no explanation as to why some cases remain as simple steatosis, whereas others appear to progress at varying rates to NASH, fibrosis and cirrhosis. A two-hit hypothesis

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has been suggested as a possible etiology of NASH [11,12]. Insulin resistance appears to be the most important factor in the development of NASH. Insulin resistance leads to fat accumulation in the hepatocytes by two main mechanisms: lipolysis and hyperinsulinemia. It has been established that net retention of lipids, mainly triglycerides (the initial hit), within the hepatocytes is a prerequisite for the development of NAFLD. It is suspected that lipid perioxidation and oxidative stress, leading to the formation of free radicals (the second hit), are the principal culprits in producing hepatic necro-inflammation [11,12]. There may be additional metabolic or genetic defects rendering the liver more susceptible to injury from oxidative stress in those individuals who progress to NASH [13–19]. Serum adiponectin is reduced in children with elevated ALT, similar to adults. However, children with presumed NAFLD lack the elevation in proinflammatory cytokine levels as seen in adults [20]. This suggests that depressed levels of adiponectin play a more proximal role than circulating proinflammatory cytokines in the development of NAFLD in children [20]. The role of TNF-α and/or leptin in predicting the degree of liver involvement in children with NAFLD was evaluated in a recent study by Manco and colleagues [21]. In their study, serum levels of TNF-α and leptin were measured, and NAFLD activity score (NAS); (NAS > 5 is diagnostic of NASH) was computed in 72 consecutive biopsy-proven NAFLD cases. Rigorous analysis showed that TNF-α ($p < 0.0001$), leptin ($p = 0.001$), triglycerides ($p = 0.013$) and alkaline phosphatase ($p = 0.046$) levels were significantly associated with a NAS of 5 or more. TNF-α and leptin levels accurately predicted the risk of NAS of 5 or more in over 80% of the cases. TNF-α alone or combined with leptin emerged as a specific and accurate laboratory marker of NASH in a simple risk score [21].

NAFLD was initially considered a stable condition. However, recent reports in adults suggest NASH progressing to end-stage liver disease in a significant proportion of patients with a high risk of hepatic failure and hepatocellular carcinoma [22–24]. Metabolic syndrome, a disorder characterized by the presence of insulin resistance, hyperlipidemia, hypertension and abdominal fat distribution, has been studied for the associated risk of NASH and steatosis in adults [12,25,26]. The risk increased from one to 99-fold with each addition of the four components [27]. Some hypothesize that NASH is a disease of genetic etiology [16–19] and is the hepatic manifestation of the metabolic syndrome [28–30]. Furthermore, familial aggregation of NASH has also been observed [9,18].

Diagnosis of NASH & NAFLD

Clinical presentation of NASH is often quite subtle, as most patients are initially asymptomatic with an incidental finding of elevated transaminases and truncal adiposity [7]. Some patients may have right upper quadrant fullness/pain, hepatomegaly, gall stones, fatigue, depression and acanthosis nigricans [10,31]. Diagnosis of NASH should only be made after excluding alcohol abuse, viral, autoimmune, genetic, drug-related, toxic or other etiology of liver disease.

The diagnostic evaluation of NAFLD in children is contingent upon the detection of hepatomegaly or elevated serum aminotransferases by primary care providers (PCPs). Therefore, awareness and identification of overweight children with hepatomegaly and/or elevated liver enzymes by the PCPs is crucial for early diagnosis and management of NAFLD. Patton *et al.* studied the physical examination findings and subsequent diagnostic testing ordered by 18 physicians on 11 obese school-aged children [32]. Several children in that group had hepatomegaly and NAFLD. In those with NAFLD, clinicians detected hepatomegaly in 1.4% of encounters and requested serum liver chemistries in 12.5% of encounters. This suggests that increased awareness for pediatric NAFLD by PCPs and specialists is needed. Difficulty in the detection of hepatomegaly by physical examination in obese children may also contribute to the delay in diagnosis by physicians [33]. The presence of obesity should alert a PCP to screen for NAFLD by evaluating laboratory tests; however, it is important to remember that NAFLD can occur in normal-weight subjects and with normal transaminase levels [34]. Similarly, Riley *et al.* reported that the majority of overweight children identified on retrospective chart review were not diagnosed by general pediatricians or pediatric subspecialists, and did not receive relevant and recommended evaluations or interventions, especially below 5 years of age [35].

The relationship between hepatic fat content and adipose tissue distribution (determined by magnetic resonance imaging) was investigated by Fishbein *et al.* in a retrospective review of obese children undergoing evaluation for NAFLD [36]. Significant correlation was observed between hepatic fat fraction

(HFF) and visceral adipose tissue content in those children, but not to body mass index (BMI) or subcutaneous adipose tissue content. Elevated serum ALT was associated with a higher HFF. Therefore, visceral adiposity is a risk factor for pediatric NAFLD, as in adults [36]. In a recent study, Manco *et al.* reported that abdominal rather than generalized obesity contributed to liver fibrosis in a group of 197 consecutive Caucasian children with NAFLD. Waist circumference was the only component of the metabolic syndrome to be associated with fibrosis in these children. Therefore, they urged that the presence of abdominal obesity can be an additional criterion for the selection of children and adolescents who should undergo extensive investigation, including liver biopsy [37]. Furthermore, NASH is more likely to develop in obese, insulin-resistant pubertal male adolescents of Hispanic ethnicity and Caucasians [38,39].

Currently, there is no collective definition for the metabolic syndrome in children or adolescents [40]. Table 1 summarizes the variables most commonly utilized to establish pediatric metabolic syndrome score. Recent estimates indicate that approximately 2–10% of young people possess the metabolic syndrome phenotype. In a large, multiethnic, multiracial cohort of children and adolescents, Weiss *et al.* reported that the prevalence of the metabolic syndrome increased with the severity of obesity and reached 50% in severely obese patients [41]. Since there is no clear definition and the prevalence rate is relatively low, several authors have derived a continuous score representing a composite risk factor index [42]. An overview of the origin and utility of the continuous metabolic syndrome score in pediatric epidemiological research has been reported by Eisenmann and colleagues [42]. In a recent study of the prevalence of metabolic syndrome in American adolescents, de Ferranti and colleagues proposed a definition of pediatric metabolic syndrome using criteria analogous to the third report of the Adult Treatment Panel III [43].

The relationship between NAFLD and cardiovascular risk factors, such as the metabolic syndrome in children, is also not fully understood. In a case–control study of 150 overweight children with biopsy-proven NAFLD and 150 overweight children without NAFLD, Schwimmer and colleagues compared rates of the metabolic syndrome using Adult Treatment Panel III criteria [44–46]. Cases and controls were well matched for age, sex and severity of obesity.

Table 1. Components of metabolic syndrome in overweight adolescents*.

Risk factors	Defining level
Body mass index	>97th percentile
Systolic or diastolic blood pressure	>95th percentile
Impaired glucose tolerance	>140 mg/dl‡
Triglycerides	>95th percentile
High-density-lipoprotein cholesterol	<5th percentile

**Defined by three or more gender and age specific components.*
‡2 h blood glucose after standard oral glucose load.
Adapted from [31].

Children with NAFLD had significantly higher fasting glucose, insulin, total cholesterol, low-density lipoprotein cholesterol, triglycerides, systolic and diastolic blood pressure, and significantly lower high-density lipoprotein cholesterol than overweight and obese children without NAFLD. After adjustment for age, sex, race, ethnicity, BMI and hyperinsulinemia, children with metabolic syndrome had 5.0–times the odds of having NAFLD than those classified as overweight and obese children without metabolic syndrome. Thus, it appears that NAFLD in overweight and obese children is strongly associated with multiple cardiovascular risk factors. Limitations of this study include the following [44]:

- Likely misclassification of some subjects having NAFLD as normal controls;
- Cross-sectional design allowing only association rather than causation;
- The possibility that some difference in insulin sensitivity between cases and controls could have been attributable to differences in Tanner stage;
- Unclear generalizability to overweight black children, because they are known to have high rates of diabetes yet low rates of NAFLD;
- Inability to resolve many issues regarding the definition and significance of metabolic syndrome in children and adolescents.

Radiological evaluation of NASH

Radiological studies for evaluation of fatty liver include ultrasound, abdomen CT scan and magnetic resonance imaging (MRI). Ultrasound findings in NAFLD include brightness of the liver, blurred vessels and increase of the liver–kidney contrast ratio. Imaging with ultrasound lends specificity of 93% and sensitivity of 89% in NAFLD. However, with progression to fibrosis and cirrhosis, ultrasound sensitivity

and specificity decrease to 77 and 89%, respectively [47]. CT scan appearance of NAFLD is suggested by decreased density of hepatic parenchyma [48]. Hepatic steatosis is diffuse in most patients, but on occasions it is focal, and ultrasound or CT scan may misinterpret it as a malignant liver mass. In such cases, MRI can distinguish space occupying lesion from focal fatty infiltration or focal fat sparing in a heterogeneous liver. It should be noted that abdominal CT, although widely used in research studies of adult liver steatosis, should play no role in the clinical management or research of pediatric NAFLD, given the significant cumulative risk of ionizing radiation and availability of alternative modalities [49].

One study evaluated hepatic steatosis severity in 50 obese children using MRI and ultrasound to compare and correlate imaging findings with clinical and metabolic characteristics of the obese children population [50]. They had hepatomegaly and/or elevated aminotransferases. Assessment of HFF by three radiologic modalities utilizing MRI, dual-energy x-ray absorptiometry scan measurement and liver ultrasound were compared. Biochemical testing, including fasting blood levels of glucose, insulin, leptin, aminotransferases and serum lipid profile, was performed. On multiple regression analysis, the most powerful predictors of elevated ALT, after correction for age, gender, BMI and pubertal status, were insulin resistance ($p < 0.01$) and MRI HFF ($p < 0.0001$). Overall, MRI was more valuable than ultrasound for the monitoring of young patients with hepatic steatosis [50]. Similarly, the ability of ultrasound to identify low grades of fat accumulation in liver has been poor compared with MRI in children, whereas; for detecting higher grades of fat accumulation, it is helpful [51].

Radiological evaluation of NAFLD may also include the use of transient elastography. This technique has received increasing attention as a means to evaluate disease progression in chronic liver disease patients. Nobili *et al.* evaluated the accuracy and reproducibility of transient elastography for the diagnosis of fibrosis in pediatric nonalcoholic steatohepatitis. They reported transient elastography to be an accurate and reproducible methodology to identify pediatric subjects without fibrosis or significant fibrosis, or with advanced fibrosis. In patients where likelihood ratios are not optimal to provide a reliable indication of the disease stage, liver biopsy should be considered when clinically indicated [52].

Role of liver biopsy in diagnosis of NASH/NAFLD

Liver biopsy is the gold-standard for diagnosis and histological evaluation of NAFLD [53,54]. Biopsy not only confirms the diagnosis, it also helps to grade the classification and severity of steatohepatitis. Histopathological studies have underscored the fact that not all obese and/or diabetic individuals with elevated liver tests have fatty liver disease. Other conditions, such as hepatic glycogenosis and hepatosclerosis, have been documented in nonobese diabetics and may represent microangiopathy of the liver [55]. Some children have hepatic fibrosis at the time of NAFLD diagnosis on biopsy [56]. Steatosis and steatohepatitis have also been observed in atypical situations, such as in lean individuals, individuals with normal liver tests, patients taking certain medications, patients with co-existent serologically diagnosed liver disease, and in very young patients. Biopsy studies have shown that the lesions of NASH may or may not persist into cirrhosis; prior evidence of NASH on liver biopsy serves as a benchmark for the concept that many cases of otherwise cryptogenic cirrhosis developed from NAFLD/NASH. Hence, liver biopsy is essential in clinical practice to establish the diagnosis of NAFLD in the pediatric population. Since definitive diagnosis of NASH usually requires histological evaluation of liver biopsy, the development of noninvasive surrogate markers and improved accuracy of imaging technology could significantly aid in the screening of large populations at risk for NAFLD.

Histological features of NAFLD/NASH

Histological features of NASH are indistinguishable from those of alcoholic steatohepatitis. Macrovesicular steatosis, lobular hepatitis with hepatocyte ballooning and necrosis, degeneration and fibrosis predominates. There is often mixed inflammatory cell infiltration (polymorphonuclear leukocytes and lymphocytes), glycogen nuclei and Mallory's hyaline in the hepatic parenchyma. Portal tract inflammation is prominent in the early stages of NASH in children, but usually absent in adults. Collagen is laid down around the central veins and perisinusoidal regions in acinar zone three, which is unique to NASH. These histological changes are often observed during the progression of simple steatosis to NASH. Current discussions in hepatic pathology include the identification of lesions of concern for progression, reproducible methods of diagnosis and semiquantification of lesions, and appropriate

nomenclature. Brunt and colleagues proposed a system of grading and staging for NASH that follows methods of separate assessment for necroinflammatory lesions (grade) and fibrosis (stage) accepted in other forms of nonbiliary chronic liver disease [54,57]. Recently, the Pathology Committee of the National Institute of Diabetes, Digestive and Kidney Diseases NASH Clinical Research Network has proposed a system of evaluation that encompasses the entire spectrum of NAFLDs from steatosis to steatohepatitis with fibrosis for use in upcoming treatment trials [54].

Schwimmer and colleagues reported two discrete histological patterns of NASH, with distinct clinical and demographic features in the pediatric population [38]. Their study included 100 consecutive children aged between 2 and 18 years of age with biopsy-proven NAFLD diagnosed from 1997 to 2003. The two forms of steatohepatitis identified on biopsy are type 1 (17% of subjects), characterized by steatosis, ballooning degeneration and perisinusoidal fibrosis, and type 2 (51% of subjects), characterized by steatosis, portal inflammation and portal fibrosis. Simple steatosis was seen in 16% of subjects and advanced fibrosis in 8% of subjects, mostly type 2 NASH. Type 1 NASH was more common in Caucasian girls and type 2 NASH was more common in boys ($p < 0.01$), ethnic minority groups (i.e., Native American, Hispanic and Asian children) and in advanced fibrosis cases. Uniform adoption of these two distinct subtypes of pediatric NAFLD for interpretation of liver biopsies will help in future studies to evaluate natural history and response to treatment.

Another study by the same group has described the clinical characteristics of NAFLD in children, including insulin resistance, and has tested correlations with liver pathology. In a retrospective review of children with biopsy-proven NAFLD, significant predictors of liver pathology were identified as ALT, BMI and fasting insulin. Thus, it is urged that children being evaluated for NAFLD be screened for insulin resistance, which is nearly universally present and correlates with liver histology [53].

Liver biopsy remains an invaluable tool to study long-term outcome of NAFLD, in order to determine if 'simple steatosis' is nonprogressive and benign or progressive leading to further complications [58].

Treatment of NAFLD

While the optimal treatment of pediatric NAFLD has yet to be determined, lifestyle modification through diet and exercise should be attempted in all children diagnosed with NAFLD [59]. Exercise programs and aerobic training have been associated with improved outcome in several patients without significant weight loss, which probably related to improvements in cardiac fitness and oxygen utilization. DuBose and colleagues reported that aerobic fitness reduced metabolic syndrome scores in obese children [60]. They examined the combined influence of aerobic fitness and BMI on the metabolic syndrome score in 375 children, who were aged 7–9 years after categorizing them as being normal weight, at risk for overweight and overweight on the basis of BMI and aerobic fitness. Participants were categorized into six BMI fitness levels. High-density lipoprotein cholesterol and triglyceride levels, insulin resistance, blood pressure and waist circumference were used to create a continuous metabolic syndrome score. Both BMI and fitness level were associated with the metabolic syndrome score. In general, the metabolic syndrome score increased across the categorized groups, with the normal-weight, high-fit group having the lowest metabolic syndrome score, and the overweight, unfit group having the highest metabolic syndrome score. Children who were at risk for overweight and had high fitness had a lower metabolic syndrome score compared with those at-risk-for-overweight, less-fit children, and the score was similar to that of the less-fit, normal-weight children. Furthermore, a high fitness level resulted in a lower metabolic syndrome score in overweight children compared with overweight children with low fitness. High fitness level modified the BMI impact on the metabolic syndrome score in children in this study. Therefore, increasing a child's fitness regardless of weight loss could reduce the risk of obesity-related comorbidities [60].

Manco *et al.* evaluated exercise capacity and insulin resistance in male children and adolescents with NAFLD and obese controls. Both children with NAFLD and obese controls had impaired heart rate response to exercise. However, obese controls were not able to reduce peripheral resistance during the test. Children with NAFLD were the most insulin-resistant. They propose that, in obese children with or without NAFLD, increased insulin resistance and bodyweight may induce cardiovascular compensatory changes in response to physical exercise with possibly different mechanisms, which are likely to be dependent on the different degree of insulin resistance [61]. In a recent randomized, controlled trial, Nobili and colleagues evaluated the efficacy of lifestyle

intervention with or without antioxidant therapy in pediatric NAFLD. Lifestyle intervention with diet and increased physical activity induced weight loss, and was associated with a significant improvement in liver histology and laboratory abnormalities in their group of pediatric NAFLD. A-tocopherol plus ascorbic acid used as antioxidants did not seem to increase the efficacy of lifestyle intervention alone [62]. However, in an open-label pediatric pilot study, Lavine reported that daily oral vitamin E administration normalized serum aminotransferase and alkaline phosphatase levels in obese children with NASH without significant change of their BMI before and after treatment [63]. In an another open-label, small observational study over a 2-year period, Nobili *et al.* reported that metformin did not appear to be more effective than lifestyle intervention in ameliorating levels of aminotransferases, steatosis and liver histology in ten children with NAFLD [64].

Pharmacologic agents evaluated in adults with NASH have not been universally effective. Several pilot therapeutic trials in adults with agents such as vitamin E, ursodeoxycholic acid, betaine, metformin and the thiazolidinediones (pioglitazone, troglitzaone and rosiglitazone) have shown quite promising improvement in the liver tests and histology [63,65–72]. However, other pilot studies evaluating the effects of other therapeutic agents, such as vitamin B complex, vitamin C, lecithin, β-carotene, selenium and treatment with gemfibrozil, on small groups of patients with documented NASH have failed to show statistically significant benefits or consistent improvement on follow-up [73]. Similarly, there are currently no proven therapies for NAFLD in children. Treatment of NAFLD in Children, the first multicenter clinical trial of vitamin E (α-tocopherol) and metformin in pediatric NAFLD, is currently in progress. Such studies are imperative to address fundamental questions regarding cause and cure.

Natural history & prognosis of NAFLD & NASH

Although NAFLD is the most common chronic hepatic disorder seen in pediatric hepatology practice, natural history of pediatric NAFLD is not known. A-Kader *et al.* recently reported a retrospective single-center experience on the progression and natural history of children diagnosed with NAFLD [3]. The entire spectrum of histological features of NAFLD was seen even in children with normal liver enzymes. Fibrosis was present in approximately 20% of those patients at diagnosis and in 40% in those with normal liver enzymes. On follow-up biopsy for patients with initial fibrosis, there was no change in 45%; another 40% had progression of fibrosis, whereas 15% had regression or disappearance of fibrosis after losing weight.

In a meta-analysis of five series of 257 adult NAFLD patients followed for 3–11 years with serial liver biopsies, 28% showed progression of pathology, 59% showed no change and 13% actually have improved histology [74]. NAFLD comprises of a wide clinical spectrum, from those with a stable mild disease, to those with a progressive hepatic inflammation, cirrhosis and liver failure in some.

Special concerns regarding pediatric NAFLD

Childhood NAFLD appears to be somewhat different from adult NAFLD. In addition to the histological and prognostic differences, children are more prone to failure of weight reduction, adolescent experimentation with illicit drugs, depression and possible additional underage alcohol consumption. It is prudent to caution that, with apparent histological distinction between pediatric and adult NAFLD, it may not be entirely accurate to simply extrapolate from adult natural history, pathogenesis and treatment data to children. As highlighted by Patton and colleagues recently, an increase in public awareness for early recognition of childhood obesity and its related morbidities is essential [32].

Conclusion

Nonalcoholic steatohepatitis is present in both children and adult populations. Insulin resistance and oxidative stress have critical roles in the pathogenesis of NAFLD. Although simple steatosis has the best prognosis within the spectrum of NAFLD, it has the potential to progress to steatohepatitis, fibrosis and even cirrhosis with end-stage liver failure. Liver biopsy remains the most reliable means of diagnosis, grading and prognostication. Lifestyle modifications such as weight loss and exercise may improve liver disease. No effective medical therapy is currently available for all patients with NAFLD.

Future perspective

Uniform criteria for early identification of obesity with or without NAFLD are necessary to initiate proactive preventive measures for improved care. There is an urgent need to develop noninvasive markers for diagnosis and to follow the course of this condition.

Since liver biopsy is the most accurate method of determining severity and staging of NAFLD, and therapeutic trials for NASH rely on sequential histological evaluation as the most convincing parameter to document effects of treatment, consensus-based criteria must be developed to assess histology.

Multicenter prospective clinical trials to assess treatment of pediatric NAFLD are imperative to address fundamental questions regarding cause, prevention and cure.

Determining the pathogenesis of pediatric NAFLD is likely to enhance our understanding of NAFLD in all age groups and may identify new treatment opportunities, as well as effective ways to prevent pediatric NAFLD.

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Executive summary

- Nonalcoholic steatohepatitis/nonalcoholic fatty liver disease (NASH/NAFLD) is commonly associated with childhood obesity. Steatosis or steatohepatitis has also been observed in atypical situations such as lean individuals or in individuals with normal liver tests.
- Assessment of waist circumference and/or waist:hip ratio should be considered a part of well-child visits, as should liver enzymes and possibly ultrasound in obese children.
- This is currently underdiagnosed by healthcare providers, therfore increased awareness of this association will prevent delays in diagnosis and treatment for asymptomatic children.
- Liver biopsy remains essential for diagnosis, staging and prognostication of NASH. Therapeutic trials for NASH rely on sequential histological evaluation as the most convincing parameter to document the effect of treatment.
- The identification of NAFLD in a child should prompt global counseling to address nutrition, physical activity and avoidance of smoking to prevent the development of cardiovascular disease and Type 2 diabetes mellitus.
- The rising childhood obesity rate with early-onset NASH may result in an epidemic of cirrhosis due to NASH in young adults with possible further complications. Thus, prevention of childhood obesity and early intervention for other risk factors may be a more cost-effective approach.

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