

Review article: epidemiology, pathogenesis and potential treatments of paediatric non-alcoholic fatty liver disease

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SUMMARY

Background

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of paediatric liver disease. Similar to NAFLD in adults, NAFLD in children is associated with obesity and insulin resistance and requires liver histology for diagnosis and staging. However, significant histological differences exist between adult and paediatric NAFLD to warrant caution in extrapolation of adult data.

Aim

To review the available data on the epidemiology, pathogenesis, diagnosis and treatment of paediatric NAFLD.

Methods

Relevant articles were identified by Medline searches using the keywords: nonalcoholic fatty liver disease, steatohepatitis, obesity and children.

Results

The rise in childhood obesity has been accompanied by an increase in paediatric NAFLD. Age, gender and race/ethnicity are significant determinants of risk, and sex hormones, insulin sensitivity and adipocytokines are implicated in the pathogenesis of paediatric NAFLD. There is no consensus for treatment of NAFLD; however, data suggest that diet, exercise and some pharmacological therapies may be of benefit.

Conclusions

To evaluate and effectively treat paediatric NAFLD, the pathophysiology and natural history of the disease should be clarified and non-invasive methods for screening, diagnosis, and longitudinal assessment developed. Randomized, controlled, double-blind trials of pharmacological therapies in children with biopsy-proven disease are necessary.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of liver disease in children. Closely associated with obesity and insulin resistance, the prevalence of NAFLD is apparently increasing in proportion to the expanding prevalence of childhood obesity. NAFLD is a clinico-pathological diagnosis characterized by macrovesicular steatosis in hepatocytes, occurring in the absence of other causes of chronic liver disease. It ranges from simple steatosis to non-alcoholic steatohepatitis (NASH) to cirrhosis. Importantly, histological features of NASH differ in adults and younger children. Extrapolation of conclusions obtained in adults may lead to errors in diagnosis or treatment of children.

EPIDEMIOLOGY

Reports of paediatric fatty liver disease in children have increased over the past three decades. However, the true prevalence of NAFLD in children remains uncertain because of lack of population-based studies and the lack of reliable surrogate screening methods. Certain diagnosis requires liver biopsy, which is impractical for a population-based study. Therefore, most studies have been limited to the use of indirect measures such as elevated serum alanine aminotransferase (ALT) and ultrasound to predict histological outcome.¹

The existing population-based prevalence studies suggest that NAFLD is a global problem with reports published in North and South America, Europe, Australia and Asia. In the United States, data from NHANES III ($n = 2450$ children, age range, 12–18 years) found an elevated ALT in 75 (3%) of adolescents.² The 1998 Korean National Health and Nutrition Examination Survey ($n = 1543$, age range 10–19 years) found a similar prevalence of elevated ALT (3.2%) and a study of Japanese children ($n = 810$, age range 4–12 years) reported NAFLD in 2.6% of the population using ultrasound.^{3, 4} Studies of obese adolescents conducted in Europe, America and Asia indicated that the prevalence of NAFLD was between 10% and 77% suggesting that obesity is a major risk factor for NAFLD.^{2, 5–7} In all reports of children with NAFLD, boys outnumber girls in a 2:1 ratio.⁸

A children's autopsy study performed to estimate the prevalence of NAFLD in the United States by liver histology found that fatty liver was present in 9.6% of

children aged 2–19 years.⁹ Fatty liver prevalence increased with age, ranging from 0.7% for ages 2–4 years and up to 17.3% for ages 15–19 years. The most prominent risk factor for fatty liver was obesity (38%). Race, ethnicity and z-score significantly predicted the presence of fatty liver, with hispanics having the highest risk and African Americans the lowest risk.

HISTOPATHOLOGY OF PAEDIATRIC NAFLD/NASH

Histology is required for the definitive diagnosis of NAFLD. In many cases, features and patterns of NASH differ between adults and children.¹⁰ The traditional findings in adults, which are designated in children as 'type 1' include a combination of macrovesicular steatosis with ballooning degeneration, lobular inflammation with or without pericellular fibrosis localized primarily in acinar zone 3. Paediatric 'type 2' NASH is characterized by macrovesicular steatosis with portal inflammation and/or fibrosis, generally without evidence of cellular injury or lobular inflammation. Type 1 and type 2 NASH are distinct subtypes of paediatric NAFLD associated with different clinical, demographic and possible pathophysiological features. A comprehensive study of NAFLD in children aged 2–18 years found that type 2 NASH was present in 51% of the cohort and type 1 NASH in 17%.¹⁰ Majority of children with advanced fibrosis demonstrated a type 2 pattern. They tended to be younger and more obese than those with a type 1 pattern. Boys were significantly more likely than girls to have type 2 NASH. Children of Asian or Native American race and those of Hispanic ethnicity predominantly demonstrated type 2. These subtypes may have implications for understanding the genetics, natural history or response to treatment in paediatric NAFLD. Among children with type 2 NASH, it is not known whether the pattern evolves into the more characteristically adult type 1 pattern as the children grow older.

DIAGNOSIS OF NAFLD/NASH

In clinical practice, the diagnosis of NAFLD is usually suspected upon finding elevated serum ALT and/or evidence of fatty liver on radiographic studies. NAFLD is a diagnosis of exclusion that requires proper consideration of historical and clinical features. Other forms of liver disease including hepatitis B and C, Wilson's

disease, α -1-antitrypsin deficiency, autoimmune hepatitis, drug-induced liver injury (valproate, methotrexate, tetracycline, amiodarone, prednisone) and total parenteral nutrition need to be excluded. Typical mean presentation is in overweight children between the ages of 11.6 and 13.5 years with a higher incidence in boys.^{11–13} Most children are asymptomatic. Some have vague abdominal pain (prevalence, 42–59%), although this complaint may bias pursuit of serum measurements to find an otherwise asymptomatic condition.^{11, 13} Hepatomegaly can often be detected on abdominal examination, but is frequently missed in clinical practice. Acanthosis nigricans, a velvety brown-to-black pigmentation in skin folds and axillae, typically associated with hyperinsulinaemia can be found in up to 50% of children with NASH.^{12, 13} A family history of NAFLD may also be relevant because familial clustering is common.¹⁴

BIOMARKERS OF NASH

The most widely accepted model for the progression of simple steatosis to NASH is based on the effects of oxidative stress on biological processes within the liver capable of triggering substantial lipid peroxidation and subsequent inflammation, apoptosis and fibrosis. Several serum biomarkers of oxidative stress, inflammation, apoptosis and fibrosis are being tested, but the clinical utility of these tests remains to be determined. To assess oxidative stress in the liver, several groups have measured systemic levels of stable lipid by-products of reactive oxygen species (ROS) activity such as lipid peroxides and thiobarbituric acid-reacting substances or total antioxidant status.^{15–17} Although oxidative stress in NASH has been demonstrated, it is unclear whether systemic oxidative stress actually reflects oxidative stress present in the liver. Serum concentrations of the inflammatory cytokine tumor necrosis factor- α (TNF- α) positively predicted NASH in paediatric patients with advanced biopsy-proven NAFLD.¹⁸ These results, however, may not be reliable in general paediatric populations in which advanced NASH is unlikely.

Hepatocyte apoptosis is significantly increased in patients with NASH and correlates with disease severity.¹⁹ Apoptosis contributes to the progression of NAFLD to NASH and may contribute to liver fibrogenesis and the development of cirrhosis.²⁰ Caspase-generated cytokeratin 18 (CK-18) fragments, a biomarker of hepatocyte apoptosis, are significantly

elevated in the liver of NASH patients compared to controls and mirror the degree of steatosis.^{19, 21} In adults, a study comparing plasma CK-18 fragments with the expression level in the liver showed correlation with high sensitivity and specificity.²¹

Liver fibrosis suggests a more severe and protracted liver damage. Fibrosis is a dynamic process of extracellular matrix remodelling characterized by the breakdown and synthesis of collagens types I, II, and IV.²² The activation of hepatic stellate cells (HSCs) is the central event in fibrogenesis. Activated HSCs synthesize various extracellular matrix components, including fibrillar collagens, fibronectin and cytokines involved in the maintenance of inflammation and inflammatory cell recruitment.^{23, 24} Several groups have created panel markers using combinations of clinical and biochemical tests and specific markers of fibrogenesis, such as tissue growth factor-beta (TGF- β), laminin, type IV collagen and hyaluronic acid, to generate predictive models of fibrosis.^{25–30} Most studies have involved patients with chronic hepatitis C. Markers specifically tested in the adult NAFLD population have proven effective in the detection of advanced, severe fibrosis, but have a low predictive value for the presence of mild to moderate fibrosis.

IMAGING EVALUATION OF PAEDIATRIC NAFLD/NASH

Quantitative assessment of hepatic steatosis and fibrosis using non-invasive imaging techniques is highly desirable for the diagnosis, evaluation and longitudinal monitoring of NAFLD. An ideal imaging study detects and quantifies steatosis, fibrosis, inflammation and concomitant abnormalities such as iron deposition and cell injury. Implicit in this is the ability to differentiate NASH from simple steatosis. Radiological modalities currently available in clinical practice are capable of identifying steatosis, but cannot accurately quantify the degree of steatosis, grade the severity of inflammation, stage liver fibrosis, or differentiate NASH from simple steatosis.

The most commonly used imaging technique for screening patients with suspected steatosis is ultrasonography (US). Fat within the liver scatters and attenuates the US beam, producing a diffuse increase in echogenicity (brightness) of the liver parenchyma. The advantages of US include its excellent safety profile, portability, widespread availability and compared to other modalities, relatively low cost. However, US has

several important limitations: it is operator- and machine-dependent and its interpretation is subjective, resulting in inter-observer disagreement and results that are not always reproducible. US can be useful in the detection of severe steatosis, but its sensitivity decreases sharply if the degree of steatosis is less than 30% on biopsy.^{31, 32} In one clinical study in adults, US showed 60–94% sensitivity and 73–93% specificity for the diagnosis of liver fat.^{31, 33–36} In patients with morbid obesity, sensitivity lower than 40% has been reported because of the technical difficulties associated with performing US on such patients and the fat outside the liver attenuating the US beam within the liver. Coexisting liver disease (such as fibrosis and inflammation) also affects liver echogenicity, making US difficult to interpret in patients with NASH or cirrhosis. For these reasons, accurate quantification of the degree of steatosis is not feasible and US is unsuitable for monitoring disease progression.

The use of ultrasonic transient elastography by Fibroskan to measure the elasticity score (ES) may be an effective alternative test to assess fibrosis in viral hepatitis quantitatively and non-invasively.³⁷ However, measurements may be confounded by steatosis and are limited in patients with a BMI greater than 28, making transient elastography limited for assessing fibrosis in patients with NAFLD.³⁸

The development of contrast-specific US techniques and microbubble contrast agents may improve the diagnostic clinical value of US for assessment of NAFLD. Recent studies have indicated that the transit time of microbubbles through hepatic circulation can be a reliable surrogate marker of fibrosis in adults with NASH.^{38, 39} No paediatric studies have been performed at this time.

Computed tomography (CT) is widely used in research studies of adult liver steatosis. However, because of the ionizing radiation of CT, and because alternative modalities are available, CT should play no role in the clinical management or research of paediatric NAFLD.

Magnetic resonance imaging (MRI) offers several approaches for the assessment of NAFLD. The most commonly utilized technique to measure steatosis is phase shift imaging. Images of the liver are acquired in such a way that signals from fat and water are either in phase (sum) or out of phase (cancel). By comparing the signal intensity of in-phase and out-of-phase images, the presence of steatosis can be determined and the quantity roughly estimated. Modified

phase-shift imaging methods that can accurately calculate fat fractions are currently being tested.^{40–42} Early studies suggest these new methods yield precise, accurate measurements of total-liver fat content in children as well as in adults.

MRI may also potentially be used to measure liver fibrosis in NAFLD. Developing technology using contrast agents has enabled the visualization of liver fibrosis directly.⁴³ Several other approaches have been proposed for measuring surrogate markers of fibrosis, including molecular water diffusion and tissue perfusion.⁴⁴ Most recently, MR elastography, analogous to US elastography, has been proposed for measuring tissue stiffness.⁴⁵ Unlike US elastography, which measures only a 50 cm³ volume of the liver, the MR-based technique assesses the stiffness of the entire organ. Preliminary data suggest that MR elastography is suitable for measuring fibrosis in NAFLD. Current evidence suggests that the MRI is the modality most likely to achieve the goals of an 'ideal' imaging study defined above. Not only does it have the potential to measure steatosis and fibrosis in NAFLD accurately, but MRI is also rapid (data can be acquired in a single breath-hold), operator-independent, reproducible and widely available on routine clinical scanners.

Magnetic resonance spectroscopy (MRS) is a specialized form of MRI that analyses the frequency spectrum of MR signals. Because protons in fat and water resonate at different frequencies, the fat/water spectrum can be used to determine the fat/water signal ratio from which quantitative estimates of fat fractions can be derived. This technique can be used to quantify precisely lipid concentrations in liver tissue and is considered to be the most accurate method for quantifying liver steatosis, especially in the livers with less than 10% fat.⁴⁶ MRS of trace metabolites has also been proposed as a method of assessing fibrosis and inflammation.⁴⁷ Further work needs to be done on this application of MRS.

DISEASE PATHOGENESIS

The genetic and environmental factors responsible for NAFLD and the progression from simple fatty liver to NASH are incompletely characterized. A widely accepted model is the 'two-hit' process proposed by Day and James.⁴⁸ The first hit induces accumulation of fat in hepatocytes and is a prerequisite for the second hit (oxidative stress), which induces fibrosis and inflammation. Fat accumulation in the liver can be a

result of increased delivery of free fatty acids (FFAs) to the liver, impaired fatty acid metabolism by hepatocytes or increased *de novo* lipogenesis of fatty acids and triglycerides.^{49–51} Mitochondrial dysfunction probably plays a central role in the second-hit progression from simple steatosis to NASH. Various mechanisms have been proposed, including an increased production of ROS resulting in lipid peroxidation, inflammation, hepatocellular apoptosis and fibrogenesis.

Enhanced oxidative stress occurs in the liver of patients with NASH. Various oxidation pathways including mitochondrial, peroxisomal, cytochrome P450 and nitric oxide synthase may play a role in overproduction ROS and peroxidation of lipids accumulated within steatotic hepatocytes. Lipid peroxidation induces mitochondrial dysfunction, which results in a vicious cycle of further increased ROS production.^{52–55} ROS induces expression of several cytokines including transforming growth factor- β (TGF- β), tumor necrosis factor- α (TNF- α) and Fas ligand.^{56–59} The result is HSC activation and fibrosis, increased inflammation and apoptosis.

RISK FACTORS

The development of steatosis and fibrosis likely requires the coexistence of multiple factors, including genetics and lifestyle. Numerous risk factors have been identified including obesity, visceral adiposity, insulin resistance, race/ethnicity, age and gender.

OBESITY/VISCERAL ADIPOSITY

Body fat excess, primarily in the form of central obesity, is correlated with dyslipidemia, hyperinsulinaemia, high blood pressure and fasting glucose levels.^{60, 61} In studies from North America, Europe and Asia, obesity is consistently identified as a significant risk factor for NAFLD/NASH.^{4, 5, 11–13, 62–65} Higher BMI, significantly and independently of other risk factors, increases the chances of having liver fibrosis in children. The presence of obesity is associated with a three-fold increased risk in developing fibrosis compared to non-obese patients.¹³ Obesity itself is a state of increased oxidative stress. Studies in adults have demonstrated correlations between waist circumference and urinary isoprostane levels, a marker for oxidative stress.⁶⁶

Visceral obesity, which is associated with abdominal obesity, is more influential than body mass in predicting fatty liver.^{67, 68} Subjects with pronounced visceral

obesity have increased plasma FFA levels because of the increased lipolytic activity of the adipocytes and their ability to transport FFAs directly into the portal vein for conversion to TGs within the liver.^{69–72} High levels of FFAs are toxic to hepatocytes, resulting in damaged mitochondria (thus inhibiting FFA oxidation), promoting apoptosis and inflammation.

INSULIN RESISTANCE

As in adult NAFLD, insulin resistance is thought to be a critical factor in the etiopathogenesis. In fact, NAFLD is considered the hepatic manifestation of metabolic syndrome in adults. One study of obese children identified hyperinsulinaemia as the variable most strongly associated with an elevated ALT, and an evaluation of children with biopsy-proven NAFLD identified hyperinsulinaemia in 75% of subjects.^{13, 73}

Increased systemic and hepatic insulin resistance promotes high circulating FFAs. Impaired skeletal muscle and adipose metabolism of triglycerides (TG) result in increased circulating FFAs that are incorporated into liver TG. In the insulin-resistant state, *de novo* lipogenesis is increased, β -oxidation of FFAs is decreased and the synthesis and secretion of apolipoprotein B are impaired. The result is a decrease in secretion of TG from the liver as VLDL and net accumulation of TG in macrocytic vacuoles.

The adipokines leptin and adiponectin modulate insulin resistance and have been implicated in NAFLD progression. Increased leptin and decreased adiponectin serum levels have been found in children with NAFLD.^{74–76} Associations between adipokine levels and the severity of hepatic steatosis and fibrosis have not been established. Leptin has been implicated in hepatic fat accumulation and liver fibrosis progression. Activated hepatic stellate cells express increased amounts of the Ob-RL receptor during fibrosis development.^{77, 78}

Adiponectin is an important adipocyte-secreted cytokine that possesses anti-inflammatory properties including modulation of inflammatory cells and down-regulation of NF- κ B. In children with NAFLD, adiponectin is positively associated with insulin sensitivity and HDL cholesterol levels and negatively associated with BMI and NAFLD.⁷⁶ Adiponectin is believed to protect hepatocytes from TG accumulation by increasing β -oxidation of FFAs while decreasing *de novo* synthesis within hepatocytes.^{79, 80} Thus, the decreased adiponectin levels found in children with NAFLD may

predispose patients to disease and disease progression.⁷⁴

RACE/ETHNICITY

Genetic factors influencing the development of paediatric NAFLD remain unknown. Children from certain ethnicities are predisposed, primarily Hispanics, Asians and indigenous Americans.⁹ A high prevalence of obesity (~40%) has been reported in Mexican-American children; however, after controlling for the severity of obesity, these children tend to have a higher rate of fatty liver disease.⁸¹ Surprisingly, African American children have a lower prevalence of NAFLD despite having increased risk factors for fatty liver such as obesity and insulin resistance.^{8, 82} It is not yet known the extent to which genetic and racial differences in NAFLD susceptibility reflect genetic or environmental factors.

GENDER

Clinical series and population-based studies suggest that NAFLD is more common in boys than in girls.^{4, 5, 8, 11, 12, 63–65, 83} Boys and young prepubertal girls (mean age 10.5 years) are more likely to have type 2 NASH, while older, pubertal girls (mean age 13.3 years) are more likely to have type 1 NASH. One explanation for this gender-based difference in fatty liver development and/or expression of NAFLD is the influence of sex hormones.

Hepatic steatosis is observed in male aromatase knockout (ArKO) mice. Oestrogen replacement reverses this phenotype by decreasing hepatic TG levels and steatosis.⁸⁴ ArKO mice treated with oestrogen from birth do not develop fatty liver. Additionally, postmenopausal women and those treated with tamoxifen for ER- positive breast cancer have an increased risk of developing fatty liver and NASH.^{85, 86} One protective effect of oestrogen may be mediated through its effect on fat distribution. Oestrogen promotes the use of lipids as a source of energy and nonvisceral fat distribution, making women less likely than men to distribute excess body fat in the intra-abdominal compartment.^{87–89}

Oestradiol is also a potent endogenous antioxidant that may play a protective role in the progression of NAFLD to NASH by limiting hepatic fibrosis, inflammation and apoptosis. Oestradiol reduces lipid peroxide levels in the liver and serum.^{90, 91} In cultured rat

HSCs, oestradiol inhibits ROS generation and HSC activation/proliferation.^{92, 93} Oestradiol treatment has also been shown to suppress early apoptosis and hepatic fibrosis in male rats.⁹²

In the adult population, males are about three times more likely to develop hepatocellular carcinoma (HCC) as a complication of chronic liver disease, including NAFLD.⁹⁴ HCC, the most common primary liver cancer, is an inflammation-linked cancer associated with increased serum concentrations of IL-6 in NASH and other causes of chronic liver inflammation.^{95, 96} Oestrogen inhibits the secretion of IL-6 from Kupffer cells exposed to necrotic hepatocytes and reduces circulating concentrations of IL-6 in male mice treated with the diethylnitrosamine.⁹⁷ The gender disparity in liver cancer and inflammation may thus be because of oestrogen-dependent differences in IL-6 production.

TREATMENT

There is no consensus for treatment of NAFLD. Rational strategies aim to reduce insulin resistance, oxidative stress, or other factors involved in etiopathogenesis. Interventions may involve lifestyle changes or pharmacotherapy. Relative benefits should be assessed based on potential drug risk, or progression of untreated disease. Most studies have attempted to treat NAFLD using diet and exercise, antioxidants, or insulin sensitizing agents.

Diet and exercise

Most children with NAFLD are overweight as well as insulin resistant. First-line management for the treatment of NAFLD in this population is weight loss achieved through diet and exercise. Weight loss is the best documented therapy for diminishing elevated serum aminotransferases in presumed childhood NAFLD.^{6, 11, 65, 98–100} However, weight loss even when >10% of body weight has not proven universally effective.⁹⁹ Moreover, changes in liver histology have not been demonstrated. A major untested question is what the optimal diet for the treatment of NAFLD is. On the basis of NAFLD pathophysiology, a low-glycaemic index diet may be appropriate.¹⁰¹ A recent study of 252 overweight adults with hypertransaminasemia in a 4-week residential lifestyle modification programme showed that a reduced carbohydrate diet is associated with higher likelihood of ALT normalization after controlling for prescribed calories, baseline ALT and

weight loss.¹⁰² However, rapid and excessive caloric restrictions and weight loss may exacerbate metabolic disorders and promote hepatic portal inflammation, fibrosis, bile stasis and focal necrosis.^{103–105}

Antioxidant therapy

Antioxidant therapy decreases oxidative stress and may slow the progression of simple steatosis to NASH. Vitamin E is a nonspecific antioxidant that protects susceptible components of cellular membranes from lipid peroxidation. An open-label paediatric trial of vitamin E in dosages ranging from 400 to 1200 units per day for 2–4 months resulted in normalization of ALT in all 11 of the obese children studied.¹⁰⁶ In adults, vitamin E has been shown to reduce serum aminotransaminases and liver histology. Vitamin E is being studied as a sustained monotherapy in a double-blind, placebo-controlled trial in both children and adults as part of the National Institute of Diabetes and Digestive and Kidney Diseases-sponsored NASH Clinical Research Network.¹⁰⁷

Ursodeoxycholic acid

Ursodeoxycholic acid (UDCA) is a naturally occurring hydrophilic bile acid. It exerts cytoprotective and anti-inflammatory effects on the liver by inhibiting bile-salt mediated mitochondrial injury in hepatocytes.^{108, 109} A randomized control trial (RCT) involving 31 obese children with abnormal serum aminotransferase levels found that UDCA (10–12.5 mg/kg/day) was ineffective both alone and when combined with diet in reducing serum aminotransferases or the appearance of steatosis by ultrasonography.¹⁰⁰ Similarly, two RCTs in adults did not show beneficial effects on liver chemistry or histology.^{110, 111} Another RCT showed that 2 years of UDCA treatment in combination with vitamin E improves laboratory values and hepatic steatosis in patients with NASH.¹¹²

Insulin sensitizers

Insulin resistance is present in a majority of children and adolescents with biopsy-proven NAFLD and is thus a rational therapeutic target. Metformin, a dimethylbiguanide agent, reduces hepatic glucose production and increases insulin sensitivity in patients with type 2 diabetes.^{113–116} Safety and efficacy have been established for metformin in the treatment of diabetes in the

paediatric population.^{117, 118} Metformin has been evaluated in an open-label pilot study of 10 children with biopsy-proven NASH and elevated ALT level.¹¹⁹ After 6 months of therapy (500 mg twice per day), all subjects demonstrated a significant improvement in ALT and hepatic steatosis as assessed with MR spectroscopy. A paediatric (ages 7–17 inclusive) RCT investigating metformin as a monotherapy is ongoing in the NASH Clinical Research Network. Several pilot studies of varied design using metformin for adults with NAFLD or NASH have shown improvement in liver function tests and a decrease in liver volume.^{119–123}

Thiazolidinediones such as pioglitazone and rosiglitazone are peroxisome proliferator-activated receptor- γ agonists that increase hepatic insulin sensitivity and improve glucose and lipid utilization in type 2 diabetes.^{115, 124–126} Thiazolidinediones ameliorate insulin resistance in adipose tissues, the liver and muscle to reverse the hyperinsulinaemia, hyperglycaemia and the excessive supply of plasma FFAs to the liver associated with NAFLD.^{115, 124, 127} Thiazolidinediones also increase plasma adiponectin levels, activate AMP-activated protein kinase, stimulate fatty acid oxidation and inhibit hepatic fatty acid synthesis.^{128–130} A randomized, double-blind, placebo-controlled trial of pioglitazone showed metabolic and histological improvement in adult patients with NASH.¹³¹ In this study, diet plus pioglitazone normalized aminotransferase levels, decreased hepatic fat content, increased hepatic insulin sensitivity and was associated with improvement in histological findings with regard to steatosis, ballooning necrosis and inflammation. However, a recent meta-analysis has raised a significant concern regarding the increased risk of heart failure and cardiovascular disease associated with thiazolidinedione treatment of type 2 diabetes.¹³² Minimal safety data are available on thiazolidinedione treatment of children with type 2 diabetes and none in children with NAFLD. Thus, although treatment of adult NASH with this class of drug shows promise, the lack of safety data in children warrants restraint in using this class of drugs outside an appropriately designed and FDA-approved trial.

Pentoxifylline

Pentoxifylline (POF) is a methylxanthine compound that attenuates TNF- α production.^{133, 134} In peripheral blood, mononuclear cells from patients with NASH, POF significantly decrease LPS-stimulated TNF- α

production.¹³⁵ No studies have evaluated POF treatment in paediatric NASH patients. Several short-term, open-label trials in adults with biopsy-proven NASH appear favorable.^{136–138} In all studies, POF treatment reduced serum aminotransferases concurrent with serum TNF- α levels. An open-label follow-up study of nine patients with biopsy-proven NASH showed a significant histological improvement by repeat biopsy after 12 months of POF treatment.¹³⁸ Five of the nine patients had a significant improvement in scores for hepatic steatosis and necroinflammatory activity, while four patients demonstrated a reduction in fibrosis stage. Because the existing data are from small and uncontrolled trials, these initial results should be regarded as proof-of-concept rather than definitive studies. Larger controlled trials of longer duration are necessary to assess the long-term clinical benefits and safety of POF.

SUMMARY OF TREATMENT OPTIONS

Now, there are no conclusive results to support the use of pharmacological agents in paediatric NAFLD. Limited data on natural history with respect to cardiovascular or hepatic morbidity and mortality render assessment of pharmacotherapeutic intervention difficult. Many pharmacological therapies have shown promising results in preliminary pilot studies, but few have been examined in appropriately powered,

randomized, double-blind, placebo-controlled trials. Interpretation of most studies is complicated by the use of endpoints other than liver histology or quality of life, and none has assessed liver- or cardiac-related morbidity or mortality. Most studies involve the treatment of adult NASH, which appears sufficiently distinct from paediatric NASH to warrant caution in extrapolation.

Now, very few studies exist on the sensitivity of fatty liver to xenobiotics. The effects of NAFLD on hepatic function, specifically drug biotransformation and storage of liposoluble xenobiotics remain unknown. Several alterations in genes involved in xenobiotic transformation have been identified.¹³⁹ The sequestration of drug substrates in lipid-filled subcellular compartments of the liver may limit rates of drug oxidation and elimination apart from the dysregulation of enzymatic detoxification and neutralization capacity. Thus, fatty livers may be more vulnerable to toxic effects of xenobiotics.

Without conclusive evidence to support the use of pharmacological therapeutics and establish their safety in paediatric NAFLD, diet and regular physical activity currently remain the only reasonable and likely effective approaches to the disease.

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