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REVIEW

Fatty liver in childhood

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Abstract

Fatty liver is a growing health problem worldwide. It might evolve to nonalcoholic steatohepatitis, cirrhosis and cause hepatocellular carcinoma. This disease, which has increased because of eating habits, changes in food content and lifestyle, affects people from childhood. The most important risk factors are obesity and insulin resistance. Besides these factors, gender, ethnicity, genetic predisposition and some medical problems are also important. Cirrhosis in children is rare but is reported. Nonalcoholic fatty liver disease (NAFLD) has no specific symptoms or signs but should be considered in obese children. NAFLD does not have a proven treatment. Weight loss with family based treatments is the most acceptable management. Exercise and an applicable diet with low glycemic index and appropriate calorie intake are preferred. Drugs are promising but not sufficient in children for today.

Key words: Nonalcoholic fatty liver disease; Nonalcoholic steatohepatitis; Children; Obesity; Metabolic syndrome; Insulin resistance; Chronic liver disease

Core tip: Nonalcoholic fatty liver disease (NAFLD) consists of steatosis in liver, steatohepatitis and cirrhosis. Histological type 2 pattern (macrovesicular steatosis with portal inflammation and/or fibrosis, generally without evidence of cellular injury or lobular inflammation) is seen differently in children than in adults. The most important risk factors are obesity and insulin resistance, as well as gender, ethnicity, genetic predisposition and some medical problems. Progression to cirrhosis in children is rare but possible. NAFLD does not have a proven treatment. Losing weight and increasing physical activity provide improvement in histological and biochemical findings in fatty liver. Drugs are used in specific situations. More research is needed for drug therapy.

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INTRODUCTION

Fat is stored as triglyceride (TG) in human liver. Steatosis is defined as fat accumulation in hepatocytes and is seen in many liver diseases[1-3].

Nonalcoholic fatty liver disease (NAFLD) defines the spectrum of histological changes in liver in which macrovesicular steatosis is outstanding[3]. NAFLD includes simple hepatic steatosis due to obesity and/or insulin resistance, nonalcoholic steatohepatitis (NASH) and cirrhosis. Hepatosteatosis usually limits itself but it may advance to NASH. NASH differs from simple steatosis by hepatocyte damage, inflammatory infiltrate and collagen deposition[4-6].

In many ways, the NASH pattern and characteristics differ between children and adults[7]. In adults, common features are the combination of macrovesicular steatosis with ballooning degeneration and lobular inflammation

with or without pericellular fibrosis localized primarily in acinar zone 3 (type 1). Pediatric NASH is characterized by macrovesicular steatosis with portal inflammation and/or fibrosis, generally without evidence of cellular injury or lobular inflammation (Type 2). Type 1 and type 2 NASH are distinct subtypes of pediatric NAFLD associated with different clinical demographic and possible pathophysiological features. In children with NAFLD aged 2-18 years, 51% is type 2 and 17% is type 1. In most of the children with extensive fibrosis, type 2 pattern is demonstrated[8]. These children are younger and more obese compared to children displaying type 1 pattern. Type 2 NASH is more common in boys than girls. Asian, Native American race and those of Hispanic ethnicity predominantly demonstrate type 2. Among children with type 2 NASH, it is not known whether the pattern evolves into a more characteristically adult type 1 pattern as the children grow older[9].

There has been an increase in NAFLD frequency in the last 30 years[1,8-11]. Nowadays, NAFLD is the most common form of liver disease in children[7]. A chronic obesity associated condition, NAFLD can lead to cirrhosis and liver failure over time[8]. It is also an independent risk factor for cardiovascular disease and liver cancer[9]. Studies have demonstrated differences in NAFLD prevalence rates across race/ethnicity, gender and weight status[12-14].

EPIDEMIOLOGY

In developed countries, hepatosteatosis is seen in 20%-30% of an unselected population[15]. The prevalence of NAFLD in Hong Kong Chinese is 27.3%. Around 4% of patients with fatty liver in the community had advanced fibrosis, as estimated by transient elastography[16].

The frequency of NASH is considered to be 2%-3%. It is reported that 10%-29% of NASH cases develop cirrhosis in 10 years[17]. Cirrhosis may progress to liver cancer. Hepatocellular carcinoma may occur in 4%-27% of the individuals with NASH-induced cirrhosis[18-20].

Since childhood obesity became epidemic in developed countries, NAFLD became the most common cause of chronic liver disease in pediatrics[7].

In fact, the true NAFLD prevalence in children is unknown. A population based autopsy study reported that 13% of children and adolescents are affected with NAFLD, 23% of the subjects with NAFLD had evidence for steatohepatitis, whereas bridging fibrosis or cirrhosis was observed in 9% of the children with NASH. Overweight and obese children accounted for 81% of all of the cases of NAFLD. A male-to-female ratio was 2: 1[7,20-23].

It is suggested that NAFLD prevalence increases with age, with a mean age at diagnosis between 11 and 13 years[24]. This tendency is explained by adolescent hormonal changes which result in an increase in serum insulin levels and fat accumulation in the liver[25,26].

Obesity and insulin resistance are the most common risk factors for NAFLD. However, differing amounts of fat accumulation in individuals with similar adipose tissue suggests that other factors are also responsible. Gender, ethnicity and genetic predisposition are emphasized[27-35].

The prognosis of children with NAFLD is still unknown. Patients with simple steatosis may still develop NASH and fibrosis progression. It is reported that weight reduction is associated with non-progressive disease in adult patients[28]. It is suggested that long term survival of NAFLD pediatric patients is shorter than non-affected patients[29].

PATHOGENESIS

Triglycerides are preferred as storage nutrients in cells to regulate the changes between intake and usage. Triglycerides supply high calories. Additionally, because they are not dissolved in water, they might be stored intracellularly in high amounts without causing any colloidal or osmotic problems. Triglycerides are basic material stocks of adipocytes and are not accumulated in other cells, except in unusual situations. Steatosis in liver is not an adaptive process; indeed it may cause severe chronic problems[1].

Fat droplets should be seen in at least 5% of hepatocytes in order to be named as steatosis. Another definition is TG deposition in the liver above 95th percentile or more than 55 mg per gram of liver tissue in a healthy lean person[2].

Hepatosteatosis might be seen in two different types; macrovesicular and microvesicular. In macrovesicular steatosis, one or a few lipid droplets are present, filling the total hepatocyte. These lipid droplets propel the nucleus to the edge. In microvesicular type, multiple small lipid droplets are seen, giving a foamy appearance[3].

Microvesicular steatosis might be seen in Reye syndrome, salicylate, sodium valproate or ethanol intake, fulminant hepatitis D, mitochondrial fatty acid beta oxidation defects and urea cycle disorders. In these disorders, liver function tests are usually affected and the patient is comatose. If the patient survives, permanent damage will not occur in the liver. Macrovesicular type occurs in alcoholic liver disease, obesity, diabetes, kwashiorkor, AIDS, total parenteral nutrition therapy, phosphorus intoxication and steroid treatment[3].

High concentration of serum saturated free fatty acids is important in the pathogenesis of steatosis. This high concentration of saturated free fatty acids creates hepatotoxic impulse. Besides, esterification of these free fatty acids into TGs is a process of detoxification. The balance between TG deposition and removal is disrupted. There are three sources of fatty acids causing TG deposition in liver: from diet, 15%; *de-novo* synthesis (carbohydrates from diet), 26%; and adipose tissue circulating, 59%[1,5].

Twenty percent of the fat present in the systemic circulation (100 g/d) is taken by the liver. Daily intake of

TGs from diet (approximately 20g/d) and free fatty acids from adipose tissue (approximately 20 g/d) enter the liver as TG[1,36]. There has been an increase in NAFLD frequency in the last 30 years. It is considered that this is due to changes in the amount and content of food. Changes in food composition cause steatosis in liver. Generally, carbohydrates and fructose play the most important role in this issue. Fructose influences the dietary carbons to move to liver and participate in lipogenesis. Despite glucose, fructose is almost totally taken from the systemic circulation. Fructose is phosphorylated at C1 instead of C6 and because of this it cannot be used in glycogen synthesis. Instead, fructose is changed to glyceraldehyde-3-phosphate, which provides substrate for *de-novo* lipogenesis. Yearly fructose intake of the population is increasing day by day and consequently NAFLD incidence is rising[1,37]. As the adipose tissue increases in obesity, death receptors in adipose tissue and apoptosis pathway are activated. Increase in adipocyte death causes more macrophage migration. Insulin resistance and hepatosteatosis occur as a result. Approaches blocking apoptosis of adipose cells are considered to improve complications related to obesity, including NAFLD. Lipoapoptosis is related to AST/ALT > 1 and liver fibrosis[38-40].

Insulin stimulates fatty acid production while preventing glucose production in the liver. As insulin resistance develops in the liver, the effect of insulin on preventing glucose production diminishes. However, the effect of insulin on stimulating fat synthesis in the liver is preserved. When the insulin level decreases with therapy, steatosis in the liver also decreases. Additionally, high insulin levels increase hepatotoxicity by preventing FFA oxidation[41].

It is suggested that NAFLD pathogenesis is multifactorial with many factors affecting disease development and progression. The "multiple-hit" hypothesis is currently the established pathogenetic model[42]. At the onset, NAFLD is characterized by fat accumulation in the liver and insulin resistance, influenced by genetic susceptibility, epigenetic mechanisms, a sedentary lifestyle and hypercaloric diets[43]. Hepatic fat accumulation leads to exacerbating insulin resistance by interfering with phosphorylation of insulin receptor substrates[44]. Free fatty acid accumulation and insulin resistance predispose the fatty liver, including oxidative stress, inflammatory cytokines, stellate cells activation and mitochondrial disturbance, which lead to inflammation, necrosis and fibrosis[45]. A changing of gut microbiota and excess gut permeability increase liver exposure to gut-derived bacterial products in NAFLD. These products stimulate innate immune receptors and trigger liver inflammation and fibrogenesis[46].

Hepatic progenitor cell activation is correlated with fibrosis and NASH progression[47]. Adiponectin, leptin, resistin and tumor necrosis factor-alpha are also thought to be involved in the progression of steatosis to NASH. Adipocytes or inflammatory cells infiltrating the adipose tissue in insulin resistance are responsible for adipocytokine secretion. Leptin may activate hepatic stellate cells. The expansion of adipose tissue, especially visceral fat, is associated with a decrease in the release of insulin-sensitizing and anti-inflammatory cytokines and an increase in the release of pro-inflammatory molecules[48]. Tumor necrosis factor-α and interleukine-6 levels are elevated in the liver and blood of NASH patients. These cytokines are involved in Kupffer and hepatic stellate cell activation in myofibroblasts[49]. NAFLD results from the relationship between multiple organs, including adipose tissue, liver, gut and the pancreas[50,51].

CLINICAL FINDINGS

Most of the cases are asymptomatic but nonspecific symptoms like abdominal pain may be present[30]. The most common admission reason is slightly elevated transaminases or coincidentally noticed hepatomegaly. Multiple diseases like Wilson's disease, drug-induced liver injury and autoimmune hepatitis should be excluded before a diagnosis of NAFLD[30,31].

Obesity is distinctive[7-15,31]. In adults, 10%-75% of fatty liver occurs with insulin resistant type 2 diabetes. Fatty liver is defined in poorly regulated type 1 diabetes (Mauriac syndrome) in children. Children with typical NAFLD have insulin resistance with hyperinsulinemia but they are euglycemic. Type 2 diabetes mellitus is present in 5.5% of NASH cases[15,32]. Acanthosis nigricans, defined as hyperplasia of pigmented skin cells, is an important physical examination seen with insulin resistance. This can be found in more than 50% of children with NASH. Family story is important in NAFLD because familial clustering is common[33-35].

Obesity is reported, especially after ALL chemotherapy, hypothalamic dysfunction or hypothalamic surgery. Even NAFLD progressing to cirrhosis is defined in these children. NAFLD is also seen in Prader-Willi syndrome. Besides these, fatty liver may be seen concurrently with some inborn errors of metabolism and genetic diseases. Insulin resistance, obesity, type 2 DM and NAFLD progressing to cirrhosis may be seen in Alström syndrome. Liver fibrosis is reported in Turner's syndrome. Also, in lipodystrophy, cases are present with cirrhosis with liver transplantation[35,52].

LABORATORY FINDINGS

In NAFLD, serum aminotransferases are moderately high with ALT being higher than AST. Increase in AST and reversing of the AST/ALT ratio in NAFLD predicts a bad prognosis. Raised ALT and GGT levels, especially if they are within normal ranges, are found to be related to hepatic steatosis evaluated by USG or magnetic resonance imaging. Therefore, changing the normal ranges is being discussed. Serum GGT > 96.5 U/L is a marker of advanced fibrosis. Serum bilirubin levels are normal or near normal. Biochemical findings of cholestasis are

not present[32-57]. Serum IgG and nonspecific tissue autoantibodies imply autoimmunity. Mostly, the anti-smooth muscle antibody is positive at low titer[52-54].

The other markers synthesized in liver, like sex hormone binding globulin, ferritin and plasminogen activating inhibitor-1, may be used in the diagnosis of NAFLD[54]. Homocysteine levels may increase in steatohepatitis. High hyaluronic acid levels are the most powerful independent marker of severe fibrosis and distinguishes steatosis and NASH[15,55-57]. Laminin and ELF (enhanced liver fibrosis) scores may also be used. Low adiponectin with low adipokines are important in NASH diagnosis. A combination of serum adiponectin, homoeostasis model assessment of insulin resistance (HOMA-IR) and type Ⅳ collagen 7S, at cut-off limits of $\leqslant$ 4.0 μg/mL, $\geqslant$ 3.0 and $\geqslant$ 5.0 ng/mL respectively, was shown to have a sensitivity of 94% and specificity of 74% for identifying early NASH[58]. Cut-off values of HOMA-IR for insulin resistance are higher than in adults. When an obese patient loses weight, normal ALT decreases more and a decrease in HOMA-IR also occurs with insulin resistance.

Hypoadiponectinemia and high tumor necrosis factor-alpha levels were found to be related to NAFLD[59-71]. However, adiponectin and tumor necrosis factor-alpha gene polymorphism were not shown to be associated with NAFLD or significant fibrosis in Chinese people[72].

Urea, electrolytes, thyroid function tests, glucose, HbA1c and serum lipids should be controlled. The most common lipid disorder is hypertriglyceridemia. Autoantibodies, immunoglobulins, viral markers for hepatitis B, hepatitis C, cytomegalovirus and Ebstein-Barr virus are important in excluding chronic liver diseases. Chronic hepatitis C, Wilson's disease, cystic fibrosis and drug intoxication (*e.g.*, methotrexate) should especially be excluded[72].

Steatosis may be diagnosed by ultrasound, computed tomography or MRI scanning. Ultrasound, the cheapest option, has been reported to have a sensitivity of 89% and specificity of 93% for the identification of fatty liver[73]. Abdominal USG does not reflect changes in liver histology and it is not useful in distinguishing steatosis and NASH. Microvesicular steatosis is due to hereditary inborn errors of metabolism, urea cycle disorders and valproic acid toxicity, and it is more severe. USG with a good history taking and metabolic tests may be sufficient in diagnosis of microvesicular steatosis[15]. ALT and AST levels are not always in parallel with the histological state and therefore, in children with risk factors, USG should be performed even if ALT and AST are normal[74,75].

New non-invasive tests such as proton-magnetic resonance spectroscopy and transient elastography allow relatively accurate estimation of hepatic steatosis and fibrosis in the community[74-81].

Liver biopsy may be essential in the diagnosis of NAFLD and distinguishing NASH from other disorders. In obese patients, biopsy may be needed to differentiate NAFLD from hepatitis. Optimal timing for this is not certain. Some physicians delay biopsy for 3-6 mo, make the patient lose weight and perform biopsy if ALT is still high. In younger children and cases with acanthosis nigricans, biopsy may be performed but there is insufficient data for this[30,82].

TREATMENT

In childhood, fatty liver does not have a proven treatment[83]. In a meta-analysis evaluating studies on adults, losing weight is reported to improve histological activity in NASH but > 50% of the patients could not reach the estimated weight[84,85]. In the literature, results of the studies about antioxidants in NASH therapy are conflicting and heterogeneous. In studies with pentoxifylline, telmisartan, L-carnitine and polyunsaturated fatty acids, it is stated that these agents may improve different parameters (radiology, biochemistry, histology) of NASH[86-88]. Vitamin E or metformin is not efficient in fatty liver in children[89].

As apoptosis is the key pathogenic mechanism in NAFLD, antiapoptotic agents are considered to be efficient in treatment. Studies are proceeding on chemical chaperones (glycerol, 4-phenyl butyric acid, TUDCA), PUFA (decreases ER stress and cell death in liver caused by saturated FFA), protease inhibitors (pan-caspase inhibitor Z-VAD-fmk, VX-166) and kinase inhibitors[11,90-94].

Drugs increasing insulin sensitivity are also studied in NASH. Indeed, the best management of insulin resistance is losing weight but drugs are also used. In pediatric NASH, 1000 mg/d metformin decreased ALT, in 40% ALT became normal, and in 90% steatosis in liver detected by MR spectroscopy decreased 23%. Metformin is effective on SREBP-1c and it is used in adulthood NASH. If evidence of childhood obesity and insulin resistance is present, it is useful and advised to be used. It is used in childhood type 2 diabetes, PCOS and Prader-Willi syndrome[92]. Thiazolidinedione is reported to improve steatosis and inflammation but causes severe weight gain[85].

Exercise, diet and bariatric surgery improve liver histology. Standard obesity surgery is not studied in children and the effect on NAFLD is not known. None of the drug therapies in children is efficient in NAFLD[9,66,71,95,96].

Multi-disciplinary management is needed in obesity treatment. Decrease in weight normalizes transaminases and liver histology. The most acceptable strategy is lowering weight gain and regular medium level exercise. For losing weight, diets with a low glycemic index and realistic portions are helpful. Special diets bringing hyperinsulinism to a minimal level instead of standard low calorie diets are more effective in childhood obesity. Diets with low postglycemic index may be carried out longer than calorie restriction[96-98]. In the management of obesity, family based behavior therapies increase success. The other valuable factor is exercise because it decreases hyperinsulinemia[99-101].

CONCLUSION

Fatty liver is a growing health problem worldwide. It might evolve to nonalcoholic steatohepatitis, cirrhosis and cause hepatocellular carcinoma. There are two distinct subtypes of pediatric NAFLD associated with different clinical, demographic and possible pathophysiological features. In children with NAFLD aged 2-18 years, 51% is type 2 and 17% is type 1. The most important risk factors for NAFLD are obesity and insulin resistance. In general, NAFLD has no specific symptoms or signs but should be considered in obese children. The most common admission reason is slightly elevated transaminases or coincidentally noticed hepatomegaly. In NAFLD, serum aminotransferases are moderately high, ALT being higher than AST. Increase in AST and reversing of the AST/ALT ratio in NAFLD predicts a bad prognosis. Progression to cirrhosis in children is rare but possible. The treatment of this disease is not certain. It is demonstrated that decrease in weight normalizes transaminases and liver histology. Therefore, weight loss with regular medium level exercise and an applicable diet with low glycemic index and appropriate calorie intake are preferred. Drugs are promising but not sufficient in children for today.

In conclusion, since childhood obesity became epidemic in developed countries, NAFLD has become the most common cause of chronic liver disease in pediatrics. Therefore, it should be taken into consideration in obese children. After excluding other diseases, multidisciplinary management should be started for weight loss.

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