Clinically Actionable Hypercholesterolemia and Hypertriglyceridemia in Children with Nonalcoholic Fatty Liver Disease

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Objective To determine the percentage of children with nonalcoholic fatty liver disease (NAFLD) in whom intervention for low-density lipoprotein cholesterol or triglycerides was indicated based on National Heart, Lung, and Blood Institute guidelines.

Study design This multicenter, longitudinal cohort study included children with NAFLD enrolled in the National Institute of Diabetes and Digestive and Kidney Diseases Nonalcoholic Steatohepatitis Clinical Research Network. Fasting lipid profiles were obtained at diagnosis. Standardized dietary recommendations were provided. After 1 year, lipid profiles were repeated and interpreted according to National Heart, Lung, and Blood Institute Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction. Main outcomes were meeting criteria for clinically actionable dyslipidemia at baseline, and either achieving lipid goal at follow-up or meeting criteria for ongoing intervention.

Results There were 585 participants, with a mean age of 12.8 years. The prevalence of children warranting intervention for low-density lipoprotein cholesterol at baseline was 14%. After 1 year of recommended dietary changes, 51% achieved goal low-density lipoprotein cholesterol, 27% qualified for enhanced dietary and lifestyle modifications, and 22% met criteria for pharmacologic intervention. Elevated triglycerides were more prevalent, with 51% meeting criteria for intervention. At 1 year, 25% achieved goal triglycerides with diet and lifestyle changes, 38% met criteria for advanced dietary modifications, and 37% qualified for antihyperlipidemic medications.

Conclusions More than one-half of children with NAFLD met intervention thresholds for dyslipidemia. Based on the burden of clinically relevant dyslipidemia, lipid screening in children with NAFLD is warranted. Clinicians caring for children with NAFLD should be familiar with lipid management. *(J Pediatr 2018;■■:■■-■■).*

Atherosclerotic coronary artery disease is the primary cause of mortality in adults in the US, and is responsible for nearly 400 000 deaths annually.[1] The process of atherosclerosis begins in childhood and is associated with dyslipidemia.[2,3] Therefore, both the American Academy of Pediatrics and the American Heart Association recommend identifying children at risk for premature cardiovascular disease. In 2011, the revised National Heart, Lung, and Blood Institute (NHLBI) Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction[4] reinforced the importance of lipid screening in childhood and provided a pathway for lifestyle and pharmacologic interventions. In addition, they identified subgroups requiring specialized attention but did not address children with nonalcoholic fatty liver disease (NAFLD).

BMI	Body mass index
CHILD-1	Cardiovascular Health Integrated Lifestyle Diet
LDL-C	Low-density lipoprotein cholesterol
NAFLD	Nonalcoholic fatty liver disease
NASH CRN	Nonalcoholic Steatohepatitis Clinical Research Network
NHLBI	National Heart, Lung, and Blood Institute
TG	Triglycerides

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NAFLD is an emerging clinical problem in children and adolescents. With an estimated 9.6% prevalence, NAFLD is the most common cause of chronic liver disease in children,[5] and the leading cause of liver transplantation in young adults.[6-8] Cardiovascular disease is a serious extrahepatic comorbidity in patients with NAFLD, and is the most common cause of death in adults with this condition.[9-11] In children, NAFLD is also associated with multiple cardiovascular risk factors such as obesity, insulin resistance, hypertension, and dyslipidemia.[12-14] Recent pediatric NAFLD guidelines include monitoring of lipids.[15] However, the treatment of hypercholesterolemia and/or hypertriglyceridemia in children with NAFLD has not been addressed. Thus, it is unknown how many children with NAFLD require intervention for dyslipidemia. Moreover, there are no longitudinal data on lipids in children with NAFLD in response to intervention. Therefore, the primary study aim was to apply the NHLBI guidelines to children with NAFLD. Specific goals were to determine the frequency of clinical interventions needed for elevated plasma low-density lipoprotein cholesterol (LDL-C) or triglycerides (TG) and the outcomes on lipid profiles after 1 year of dietary standard of care.

Methods

The National Institute of Diabetes and Digestive and Kidney Diseases Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN) enrolled children in longitudinal cohort studies (Database and Database 2; NCT01061684) and clinical trials (TONIC; NCT00063635 and CyNCh; NCT01529268). These studies have been described[16,17] and were performed at each participating pediatric clinical center across the US (**Appendix**). The studies were approved by the institutional review boards at the participating institutions. Written, informed consent was obtained from a parent or guardian for all participants, and written assent was obtained from children. For this analysis, we included children who were ages 9-18 years of age with biopsy-confirmed NAFLD. Those without weight, height, blood pressure, or fasting lipid panels measured at the initial study visit were excluded from this analysis. Those who were already taking a statin, fibrate, or omega-3 fish oil at the time of enrollment in the study, or those who were subsequently prescribed one of these medications before 48 weeks of follow-up were excluded from the application of the guidelines as well.

Age and sex were recorded for all participants. The following medical background was obtained for all study participants: presence of diabetes mellitus type I and type II, chronic inflammatory disease (such as juvenile rheumatoid arthritis or lupus), renal disease and dysfunction, HIV status, organ transplant, and the use of any lipid-lowering medications in the preceding 6 months.

Physical measurements included height, weight, systolic and diastolic blood pressures. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. Blood pressure percentiles were computed according to *The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents.*[18] At the initial visit, fasting laboratory assays included total cholesterol, high-density lipoprotein cholesterol, LDL-C, and TG. All laboratory studies were repeated at the 48-week follow-up.

A diagnosis of NAFLD was based on liver histology with ≥5% of hepatocytes containing macrovesicular fat, and exclusion of other causes of liver disease based on clinical history, laboratory studies, and histology. Biopsy specimens were stained with hematoxylin and eosin and Masson's trichrome stains, and reviewed and scored by the Pathology Committee of the NASH CRN according to the NASH CRN scoring system.[19] Liver biopsies were diagnosed as NASH, borderline NASH, or NAFLD without NASH based on the aggregate presence and degree of the individual features of NAFLD. The diagnosis of NASH, borderline NASH, or NAFLD was made as a consensus agreement of the NASH CRN pathology committee.

NHLBI Guidelines

The 2011 revised NHLBI guidelines were applied to our study cohort. Normal plasma lipid levels in children were defined based on *The National Cholesterol Education Program (NCEP) Expert Panel on Cholesterol levels in Children*.[20] The NHLBI guidelines provide a separate decision tree for LDL-C and TG to determine the specific intervention required, based on the degree of lipid derangement (**Figures 1** and **2**). By following the NHLBI algorithms, children who met the thresholds for clinically actionable dyslipidemia were identified at baseline as being in the target LDL-C or the target TG group.

The target LDL-C pathway was applied to those with baseline plasma LDL-C of >130 mg/dL. After receiving dietary counseling, similar to that of the Cardiovascular Health Integrated Lifestyle Diet (CHILD-1) as described in the algorithm (**Table III**; available at www.jpeds.com), a repeat fasting lipid profile was obtained at the 1-year follow-up. Taking into consideration the presence of high and moderate risk factors (**Table IV**; available at www.jpeds.com), combined with the degree to which LDL-C remained elevated, children who did not achieve goal LDL-C would meet criteria for consideration of statin therapy or the intensification of a lipid-specific diet (**Table V**; available at www.jpeds.com).

The target TG pathway was applied to children with baseline plasma TG with age-specific cutoffs of >100 mg/dL for children <10 years of age, and >130 mg/dL for children 10 years of age and older. In a similar fashion, children received dietary counseling and fasting lipid profiles were obtained at the 1-year follow-up. In children who did not achieve their goal TG, the guidelines provide instructions for initiation of the CHILD 2-TG diet (**Table V**) or the consideration of pharmacotherapy.

NASH CRN Standard of Care

The NASH CRN Standards of Care Committee developed a uniform set of practices to be applied by investigators in the NASH CRN to the care of pediatric patients with NAFLD. Recommendations for dietary counseling were based on guidelines from the US Department of Agriculture; specifically, limiting the percent of daily caloric intake from saturated fatty acids to <10%, replacing these with monounsaturated and

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