Evaluation and Management of Lipids and Lipoproteins in Children and Adolescents

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KEYWORDS

• Pediatric dyslipidemia • Universal screening • CHILD-1 • CHILD-2 • Statin
• Bile acid sequestrants • Ezetimibe • PCSK9 inhibitor

KEY POINTS

- Universal lipid screening should be performed in all children aged 9 to 11 years and 17 to 21 years by measuring nonfasting non-HDL-C.
- Lifestyle modifications with the "Cardiovascular Health Integrated Lifestyle diet" and daily moderate-vigorous physical activity are the mainstay for pediatric dyslipidemia.
- Statins, or HMG-CoA reductase inhibitors, are the first-line pharmacologic therapy for children and adolescents with severe hypercholesterolemia that persists despite diet and exercise.
- Bile acid sequestrants, ezetimibe, and PCSK9 inhibitors are also available for treatment of persistent pediatric hypercholesterolemia.
- Fibrates are indicated in youth with severe hypertriglyceridemia that persists despite lifestyle changes.

INTRODUCTION

The National Heart, Blood, and Lung Institute (NHBLI) established acceptable, borderline high and high plasma lipid levels based on NHANES III (third National Health and Nutrition Examination Survey) data on cholesterol levels in more than 7000 children aged 0 to 19 years from 1988 to 1994 (**Table 1**). Borderline high values reflect the 75th percentile, except for the high-density lipoprotein cholesterol (HDL-C), for which they reflect the 25th percentile. Abnormal values reflect the 95th percentile except for HDL-C, for which they reflect the 10th percentile.

By studying patterns of lipoprotein levels throughout childhood, it is now known that levels may change based on age group. Mean low-density lipoprotein cholesterol (LDL-C) levels at birth have been reported to be 30.4 ± 10.3 mg/dL in the Bogalusa Heart

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Table 1
Acceptable, borderline, and abnormal plasma lipid and lipoprotein concentrations (mg/dL) for children and adolescents

Category	Acceptable	Borderline High	Abnormal
Total cholesterol	< 170	170–199	≥ 200
LDL-C	< 110	110–129	≥ 130
Non-HDL-C	< 120	120–144	≥ 145
Triglycerides			
0–9 y	< 75	75–99	≥ 100
10–19 y	< 90	90–129	≥ 130
HDL-C	> 45	40–45	< 40

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Adapted from Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents Summary Report. U.S. Department of Health and Human Services, National Institutes of Health. 2011.

Study; however, there are significant racial differences.[1] LDL-C levels increase in the first 6 months (mean change 43 mg/dL) but have small additional increments till age 7 years.[2] Then, until adolescence, lipoprotein levels will remain relatively stable. However, during puberty, total cholesterol (TC) and LDL-C levels will decrease until late adolescence when they begin to increase again.[3] Furthermore, it is well known that obtaining lipoprotein levels in childhood are good predictors of levels in young adulthood.[3]

SCREENING FOR PEDIATRIC DYSLIPIDEMIA

It has been well established that children with abnormal lipid levels have increased evidence of atherosclerosis, and early identification and control of dyslipidemia during youth and into adulthood will significantly reduce the risk of cardiovascular disease (CVD).[4,5] The goal of screening for pediatric dyslipidemia is to identify those children and adolescents at high risk for premature CVD, or those with an increased risk, due to dyslipidemia to intervene and provide appropriate treatment to lower these risks.

The first set of guidelines regarding dyslipidemia in the pediatric population was published in 1992 by the National Heart, Lung, and Blood Institute National Cholesterol Education Program.[6] These guidelines were largely based on the screening, diagnosis, and treatment guidelines for adults and were eventually adopted by the American Heart Association and the American Academy of Pediatrics (AAP). At that time, screening was largely based on family history of dyslipidemia or premature CVD, and further evaluation was conducted based almost exclusively on elevated LDL-C as a risk factor. These guidelines were updated by the AAP based on new evidence available in 1998 and again in 2008, but screening remained targeted to those children with certain risk factors. As new data became available, there was evidence indicating that 30% to 60% of children with moderate dyslipidemia (LDL level ≥160 mg/dL) likely secondary to familial hypercholesterolemia (FH) were missed using the selective screening approach.[7] Furthermore, more evidence was emerging suggesting that treatment of dyslipidemia in children resulted in regression of markers of atherosclerosis. A randomized controlled trial showed significant improvement in carotid intima-media thickness 5 years postinitiation of statins in the group aged 8 to 11 years compared with the group aged 12 to 18 years.[8] This finding led to the recommendations of considering a universal screening approach to identify those children with possible genetic dyslipidemia, intervening

sooner to achieve improved outcomes, and identifying those children with dyslipidemia associated with lifestyle and obesity.

Universal Screening

In 2011, the NHLBI and the AAP published an updated set of evidence-based guidelines for pediatric dyslipidemia including updated guidelines for screening (**Table 2**). These guidelines recommend universal screening for all children aged between 9 and 11 years, and between 17 and 21 years, because the TC and LDL-C can decrease as much as 10% to 20% during puberty.[9] However, if new family history is available or if there are additional risk factors, the individual should be screened. Screening should be performed by obtaining nonfasting, non-high-density lipoprotein cholesterol (non-HDL-C) levels.

Selective Screening

Target screening refers to a strategy of identifying and screening individuals with certain risk factors. The NHLBI guidelines recommend selective screening for certain

Table 2
Lipid screening recommendations in children and adolescents

Age Group	Recommendation	Grade/Recommendation Level
Birth–12 mo	No lipid screening	Grade C/recommend
2–8 y	No routine lipid screening	Grade B/recommend
	Selective screening; FLP ×2[a] if: • First- or second-degree relative with premature CVD[b] • Parent with TC ≥ 240 mg/dL or known dyslipidemia • Child has diabetes, hypertension, BMI ≥ 95 percentile, or smokes cigarettes • Child has a moderate- or high-risk medical condition (see **Table 3**)	Grade B/strongly recommend
9–11 y	Universal screening	Grade B/strongly recommend
12–16 y	No routine lipid screening	Grade B/recommend
	Selective screening; measure FLP ×2 if new knowledge of: • First- or second-degree relative with premature CVD[b] • Parent with TC ≥ 240 mg/dL or known dyslipidemia • Child has diabetes, hypertension, BMI ≥ 85 percentile, or smokes cigarettes • Patient has a moderate- or high-risk medical condition (see **Table 3**)	Grade B/strongly recommend
17–21 y	Universal screening	Grade B/recommend

Abbreviations: BMI, body mass index; FLP, fasting lipid profile.

[a] Measure FLP twice at least 2 weeks apart but within 3 months and average values.

[b] Parent, grandparent, aunt/uncle, or sibling with myocardial infarction, angina, stroke, coronary artery bypass graft/stent/angioplasty at less than 55 years in males, less than 65 years in females

Adapted from Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents Summary Report. U.S. Department of Health and Human Services, National Institutes of Health. 2011.

risk groups for individuals older than 2 years (see Table 2, Table 3). Screening should be performed by obtaining a fasting lipid profile (FLP) twice within an interval of at least 2 weeks to 3 months. An FLP includes TC, HDL-C, and triglycerides (TGs). LDL-C is calculated using the Friedewald equation LDL-C = TC (HDL-C + TG/5). This equation cannot be used if TG levels are greater than 400 mg/dL. The 2 lipid profile values should be averaged to determine whether further workup or intervention is warranted.

EVALUATION OF PEDIATRIC DYSLIPIDEMIA

Children with abnormal universal screening should have 2 additional fasting lipid panels measured, separated by at least 2 weeks but within 3 months, and the results should be averaged and compared with normal lipid values per Table 1. If abnormal, the patient should be evaluated for the underlying cause of the dyslipidemia, which may be primary or secondary (Table 4). Primary or monogenic dyslipidemias are a group of single-gene defects with mendelian transmission, characterized by extremely elevated LDL-C or TG levels. These disorders include but are not limited to FH, sitosterolemia lysosomal acid lipase deficiency, cerebrotendinous xanthomatosis, and familial chylomicronemia syndrome (type 1 hyperlipoproteinemia). Secondary causes should be ruled out before initiating treatment (see Table 4).

Combined (mixed) dyslipidemia is a common cause of dyslipidemia in the pediatric population and is characterized by elevated levels of TGs and non-HDL-C and decreased levels of HDL-C. This pattern has been associated with childhood obesity and shown to be related to vascular dysfunction and cardiovascular events in adulthood.[10] Combined dyslipidemia has been shown to respond to lifestyle changes as described later.[11]

TREATMENT OF PEDIATRIC DYSLIPIDEMIA

Treatment options for dyslipidemia can be categorized into lifestyle changes (diet and exercise) and pharmacologic.

Lifestyle Modifications

Cardiovascular Health Integrated Lifestyle Diet-1

The NHLBI describes the Cardiovascular Health Integrated Lifestyle Diet-1 (CHILD-1) as the first-step nutritional guidelines for all children older than 2 years and for those

Table 3
Special risk conditions for selective lipid screening in children and adolescents

High Risk	Moderate Risk
Diabetes mellitus, types 1 and 2	Kawasaki disease with previous history of coronary aneurysms
Chronic renal disease, end-stage renal disease, or post–renal transplant	Chronic inflammatory disease[a]
Postorthotopic heart transplant	HIV
Kawasaki disease with current aneurysms	Nephrotic syndrome

Abbreviation: HIV, human immunodeficiency virus.
[a] Systemic lupus erythematosus, juvenile rheumatoid arthritis.
Adapted from Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents Summary Report. U.S. Department of Health and Human Services, National Institutes of Health. 2011.

Table 4
Secondary causes of dyslipidemia in pediatric patients

Endocrine/metabolic	Storage disease
Acute intermittent porphyria	Cystine storage disease
Diabetes mellitus (types 1 and 2)	Gaucher disease
Hypopituitarism	Glycogen storage disease
Hypothyroidism	Tay-Sachs disease
Lipodystrophy	Niemann-Pick disease
Pregnancy	Infectious
Renal	Acute viral/bacterial infection
Chronic renal failure	Human immunodeficiency virus infection
Hemolytic uremic syndrome	Hepatitis
Nephrotic syndrome	Inflammatory
Hepatic	Rheumatoid arthritis
Obstructive liver disease/cholestasis	Systemic lupus erythematosus
Congenital biliary atresia	Other
Alagille syndrome	Anorexia nervosa
Exogenous	Cancer survivor
Corticosteroids	Post–solid organ transplantation
Isoretinoin	Idiopathic hypercalcemia
Beta blockers	Kawasaki disease
Oral contraceptives	Klinefelter disease
Some chemotherapeutic agents	Progeria
Alcohol	Werner syndrome

children with dyslipidemias as the first-line treatment (**Table 5**). The guidelines state that fat intake in infants younger than 12 months should not be restricted without a specific medical indication. For older children, this diet limits calories from fat to 30%, calories from saturated fat to 10%, and cholesterol intake to less than 300 mg/d. The diet also includes recommendations for breastfeeding of infants as possible based on data showing decreased TC levels in adults who were breastfed as infants compared with those who were formula-fed.[12] In the Special Turku Coronary Risk Factor Intervention Project for Children (STRIP) study, families of infants starting at age 7 months were counseled on a low-saturated-fat, low-cholesterol diet similar to that of the CHILD-1 diet. This study showed that at age 3 years, those infants in the intervention group had serum cholesterol, non-HDL-C, and HDL-C concentrations 3% to 6% lower than those infants without the dietary intervention, without detrimental effects on growth and development.[13] The study further showed that serum TC and LDL-C were also lower at age 7 years.[14] A meta-analysis reviewing 37 studies between 1981 and 1997 on the effects of the dietary guidelines of the CHILD-1 diet showed a 12% decrease in the serum LDL-C concentration in all subjects.[15] These studies all show the benefits of the CHILD-1 diet on serum TC and LDL-C levels without harm to the growth and development of children. Further details regarding the guidelines of the CHILD-1 diet are listed in **Table 5**. At least 1 hour of moderate to vigorous physical activity daily should be encouraged for all children.

Cardiovascular Health Integrated Lifestyle Diet-2

If, after a 3-month trial of the CHILD-1 diet, a patient fails to reach a therapeutic goal, the patient and family should work with a dietician to implement the Cardiovascular Health Integrated Lifestyle Diet-2 (CHILD-2) diet. This more rigorous diet limits calories from fat to 30%, calories from saturated fat to 7%, and goal dietary cholesterol to 200 mg/dL or less. **Table 6** describes the CHILD-2 diet in greater detail including

Table 5
Cardiovascular Health Integrated Lifestyle Diet-1 (CHILD-1) dietary guidelines

Birth to 6 mo	Exclusively breastfeed; if unavailable or contraindicated, consider expressed breast milk or iron-fortified infant formula
6–12 mo	Continue breastfeeding until 12 mo of age (unless unavailable or contraindicated) Gradual addition of solids No restriction of fat intake unless medically indicated No sweetened beverages; encourage water
12–24 mo	Unflavored, reduced-fat milk (2% to fat free) Avoid sweetened beverages; encourage water Table foods with total fat 30% of daily kcal intake, saturated fat 8%–10% of daily kcal intake, monounsaturated and polyunsaturated fat up to 20% daily kcal intake, cholesterol <300 mg/d Avoid transfats, limit sodium intake
2–10 y	Unflavored, fat-free milk Limit/avoid sweetened beverages; encourage water Total fat 25%–30% of daily kcal intake, saturated fat 8%–10% of daily kcal intake, mono- and polyunsaturated fat up to 20% daily kcal intake, cholesterol <300 mg/d Avoid transfats, limit sodium intake Encourage high dietary fiber intake
11–21 y	Unflavored, fat-free milk Limit/avoid sweetened beverages; encourage water Total fat 25%–30% of daily kcal intake, saturated fat 8%–10% of daily kcal intake, monounsatirated and polyunsaturated fat up to 20% daily kcal intake, cholesterol <300 mg/d Avoid trans fats, limit sodium intake Encourage high dietary fiber intake

specific recommendations for both LDL-C- and TG-lowering modifications. Like CHILD-1, the CHILD-2 diet has been proved to be both safe and efficacious. The Dietary Intervention Study in Children (DISC) was a large randomized controlled trial initiated by the NHLBI in 1987 studying the long-term effects in LDL-C after initiating children on the DISC diet, which was similar to the CHILD-2 diet.[16] The trial found that the mean LDL-C was significantly lower in the intervention group without affecting growth during puberty. The same meta-analysis that reviewed the CHILD-1 dietary guidelines discussed earlier also reviewed the CHILD-2 dietary guidelines to assess for efficacy and found that LDL-C levels decreased by 16% in the intervention group.[15] The dietary guidelines for CHILD-2 include addition of plant sterols, dietary fiber, and/or omega-3 fatty acid supplementation, which are described later.

Dietary supplement with plant sterols/stanols

There is evidence to support the use of plant sterols/stanols as a supplement to lower LDL-C levels. Plant sterols/stanols are cholesterollike substances found in plants and exist in our diet as vegetable oils or margarines, seeds, nuts, yogurt, milk, and legumes. Because they are more hydrophobic, when consumed, they inhibit intestinal absorption of cholesterol by preventing incorporation of cholesterol in the micelles, therefore reducing the bioavailability of cholesterol in the bloodstream. Several meta-analyses in the adult population have shown a 7% to 12% reduction in LDL-C with use of 1.5 to 3 g/d of plant sterols.[17] The STRIP study evaluated the effect of replacement of dietary fat with a stanol-enriched margarine in 6-year-old children

Table 6
Lifestyle recommendations for persistent dyslipidemia after 3-month trial of the Cardiovascular Health Integrated Lifestyle Diet-1 diet

LDL-C Lowering	
CHILD-2-LDL diet	Total fat: 25%–30% of total calories/d Saturated fat: ≤7% of total calories/d Avoid transfat Monounsaturated fat: 10% of total calories/d Cholesterol: <200 mg/d
Plant sterols	Can consider up to 2 g/d to replace usual dietary fat sources
Water-soluble fiber	Can consider 6 g/d (2–12 y) or 12 g/d (≥12 y)
Activity	≥ 1 h moderate-vigorous physical activity with 2-h limitation on sedentary screen time
TG lowering	
CHILD-2-TG diet	Total fat: 25%–30% of total calories/d Saturated fat: ≤7% of total calories/d Avoid transfat Monounsaturated fat: 10% of total calories/d Cholesterol: <200 mg/d Reduce sugar intake Replace simple carbohydrates with complex carbohydrates
Omega-3 fatty acid	Increase dietary fish Supplement omega-3 fatty acid 1–4 g/d for TG > 200–499 mg/dL

Abbreviation: TG, triglyceride.

and found a decrease in TC and LDL-C levels by 5.4% and 7.5%, respectively.[18] Multiple other studies have seen LDL-C level lowering by 9% to 16% with the addition of a plant sterol/stanol supplementation in the pediatric population; however, long-term effects have not yet been evaluated.[19–21]

Dietary supplement with water-soluble fiber

There is evidence to support the use of water-soluble fiber, such as psyllium, to lower LDL-C levels. Data from studies evaluating the effectiveness of fiber on serum LDL-C levels range from no change to 8% reduction in the group receiving fiber.[22–25] The NHBLI recommends that water-soluble fiber psyllium can be added to a CHILD-2 diet for those children with elevated LDL-C levels at a dose of 6 g/d for children aged 2 to 12 years and 12 g/d for those aged 12 years or older.

Considering Pharmacologic Treatment

Elevated levels of low-density lipoprotein-cholesterol

When considering further treatment options, it is important that at least 2 FLPs obtained at least 2 weeks but no further than 3 months apart have been collected. The NHBLI recommends considering pharmacologic therapy when the LDL-C level is greater than or equal to 190 mg/dL after a 6-month trial of lifestyle management for children at least 10 years of age, 160 to 189 mg/dL after a 6-month trial of lifestyle management for children at least 10 years of age with a family history of premature CVD, or 1 or more high-level risk factor or 2 or more moderate-level CVD risk factors (see **Table 3**). The goal of therapy should be to lower LDL-C levels to less than 130 mg/dL. The AAP and NHLBI recommend consideration of pharmacologic therapy at 8 years for children with an LDL-C level greater than or equal to 190 mg/dL after a trial of lifestyle management if there is a clinical suspicion or genetic confirmation of FH, or

there is at least 1 high-level risk factor or risk condition or at least 2 moderate-level risk factors or risk conditions.

Elevated triglyceride

The NHBLI recommends pharmacologic therapy for hypertriglyceridemia in patients with an average fasting TG level of greater than or equal to 500 mg/dL or any single measurement of 1000 mg/dL or more in the setting of a primary hypertriglyceridemia. Pharmacologic therapy in these patients should be done in addition to the CHILD-2-TG diet to help prevent the complication of pancreatitis.

HMG-CoA Reductase Inhibitors (Statins)

Statins are the first-line pharmacologic therapy for the treatment of elevated LDL-C levels that persists after diet and lifestyle changes (**Table 7**). Statins work by inhibiting 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMG-CoA reductase), which results in upregulation of LDL receptors therefore reducing plasma LDL-C levels. Large-scale evidence on the use of statins shows a significant reduction in coronary morbidity and mortality in high-risk populations.[26,27] Statin therapy in children with FH has been shown to slow the progression of carotid intima-media thickness,[28,29] and reduce the risk of CVD.[29–33] In children, LDL-C reduction ranges from 17% to 50% from baseline and TC reduction from 13% to 39% with different statins (see **Table 7**).[34–47] Pravastatin, pitavastatin, and rosuvastatin are approved by the US Food and Drug Administration (FDA) for children 8 years and older, and all statins listed in **Table 8** are approved for children 10 years and older. When initiating statin therapy, the lowest available dose should be started once daily. Medication should be titrated within the range detailed in **Table 7**, with the goal LDL-C level less than 130 mg/dL.[48] FLP, aspartate aminotransferase, alanine aminotransferase, and creatine kinase (CK) should be checked at baseline and then repeated 4 weeks, 8 weeks, and then every 3 to 6 months after initiation of therapy.[48] If the goal LDL-C level is not reached, addition of a second agent should be considered, under the direction of a lipid specialist.

Statins are usually well tolerated in children and have an excellent safety profile.[49] A systematic review by the US Preventive Services Task Force (2014) concluded that in children with FH treated with statins, adverse events did not significantly differ in those randomized to statins compared with placebo.[50] In a meta-analysis of statin use in children, there were no significant differences in hepatic enzyme elevation in children receiving statins compared with those receiving placebo.[30] Patients should be

Table 7
Statin (HMG-CoA reductase inhibitor) initiation age and approved pediatric doses per US Food and Drug Administration

Drug	Age (years)	Dose	Effect on LDL Reduction
Atorvastatin	≥10	10–20 mg/d	30%–38%[36]
Fluvastatin	≥10	20–80 mg/d	24%–33%[35,37,38]
Lovastatin	≥10	10–40 mg/d	38%–50%[39]
Pitavastatin	≥ 8	2-4 mg/d	38%–44%[40,41]
Pravastatin	≥ 8	20–40 mg/d	23%–34%[42]
Rosuvastatin	≥ 8	5–20 mg/d	17%–36%[43–45]
Simvastatin	≥10	5–40 mg/d	25%–41%[46,47]

Abbreviation: HMG-CoA, 3-hydroxy-3-methyl-glutaryl-coenzyme A.

Table 8
Pharmacologic therapy for pediatric dyslipidemia

Type of Medication	Examples	Mechanism of Action	Major Effects	Adverse Reactions
HMG-CoA reductase inhibitors	Atorvastatin Fluvastatin Lovastatin Pitavastatin Pravastatin Rosuvastatin Simvastatin	Upregulation of LDLR by inhibiting cholesterol synthesis	↓ LDL-C	Elevated hepatic enzymes, elevated CK
Bile acid sequestrants	Cholestyramine Colesevelam Colestipol	Upregulation of LDLR by binding bile acids and stimulating hepatic bile acid production from cholesterol	↓ LDL-C	Gastrointestinal side effects, folate deficiency, vitamin D deficiency
Cholesterol absorption inhibitors	Ezetimibe	Inhibiting cholesterol absorption resulting in upregulation of LDLR	↓ LDL-C	Gastrointestinal upset, myalgia
PCSK9 Inhibitor	Evolocumab	Binds PCSK9 causing increased LDLR availability	↓ LDL-C	Headache, flulike symptoms, oropharyngeal pain, constipation
Niacin	Niacin	Inhibit DGAT2 and release of FFA, decreasing triglyceride production	↓ LDL-C	Flushing, headache, gastrointestinal upset
Fibrates	Fenofibrate Gemfibrozil	Upregulation of PPARα, causing lipolysis and decrease in triglycerides	↓ TG	Gastrointestinal side effects, myositis when used with statins
Fish oil	Omega-3 acid ethyl esters	Decreases FA and TG synthesis, increases FA degradation	↓ TG ↑ HDL-C	Unpleasant taste, gastrointestinal upset

Abbreviations: CK, creatine kinase; DGAT2, diglycerol acyltransferase2; FA, fatty acid; FFA, free fatty acid; LDLR, LDL receptor; PCSK9, proprotein convertase subtilisin/kexin type 9; PPARα, peroxisome proliferator-activated receptor.

counseled on the development of myopathy while using statins; however, the pediatric trials did not show any significant difference in the development of muscle enzyme elevations (CK > 10-fold) between those children receiving statins and those receiving placebo. Statins should be discontinued if the liver enzyme levels are greater than 3 times the upper limit of normal, CK level is greater than 10 times the upper limit of normal, or if a patient develops adverse effects to therapy. If the patient reports symptoms of myopathy (muscle pain or weakness), consider checking the CK level to assess if the statin needs to be stopped. The use of statins has been contraindicated during pregnancy and while breastfeeding, and females should be informed about the need to avoid pregnancy and breastfeeding while using statins; however, FDA has recently requested removal of the strongest warning against using statins during pregnancy.[51]

Bile Acid Sequestrants

Bile acid sequestrants (BAS) such as colesevelam, cholestyramine, and colestipol decrease LDL-C levels in the serum by binding bile acids in the intestine and preventing their reabsorption through the ileal bile acid transporter therefore stimulating the conversion of cholesterol to bile acids. To achieve this, LDL-C receptors are upregulated resulting in decreased serum LDL-C levels; they can lower LDL-C levels by 10% to 15% and can be used as a monotherapy or combined with statins if statins alone do not help to achieve target LDL-C levels.[52] These were the only class of medications recommended by national cholesterol education program (NCEP) in 1992.[6] The first-generation BAS, cholestyramine and colestipol, cause significant gastrointestinal side effects, decreased serum folate levels, and 25-hydroxyvitamin D deficiency in addition to poor tolerability.[53,54] Second-generation BAS, colesevelam, is better tolerated and is FDA approved for children aged 10 years or older.[55] Caution should be taken when other medications are used with BAS because BAS may decrease absorption of some medications.

Cholesterol Absorption Inhibitor (Ezetimibe)

Ezetimibe, a cholesterol absorption inhibitor, works by inhibiting NPC1L1, an intestinal cholesterol transporter, which results in a compensatory upregulation of endogenous cholesterol biosynthesis, which increases LDL receptor activity and therefore decreases LDL-C levels in the serum. Ezetimibe is approved by the FDA in children aged 10 years and older with heterozygous FH, homozygous FH, and sitosterolemia.[56] Ezetimibe monotherapy, dose 10 mg/d, can cause LDL-C level reduction of about 28% to 30%.[57,58] Coadministration of ezetimibe and statin can cause an additional 20% decrease in LDL-C levels compared with the use of statin alone.[59] Ezetimibe is generally well tolerated with no significant side effects, although mild gastrointestinal upset and myalgia have been reported at the daily dose of 10 mg.[57,58]

Niacin

Niacin works by inhibiting hepatic diacylglycerol acyltransferase-2, an enzyme that converts diacylglycerol to TGs, and the release of free fatty acids from adipose tissue, thus decreasing very-low-density lipoprotein (VLDL) and LDL-C production and HDL-C degradation. Niacin is not routinely used in pediatric population due to the lack of published safety data. One retrospective review, in children aged 4 to 14 years, showed that niacin reduced levels of TC by 23% and LDL-C by 30%, with no significant effect on TGs.[60] Adverse effects were significant and included flushing, abdominal pain, vomiting, and headache.[60] These well-known side effects make niacin a poorly tolerated medication even in adults. Clinical trials of niacin in combination

with a statin in adults have found serious adverse effects of infection, gastrointestinal bleeding, myopathy, and rare hepatotoxicity[61,62] (see Connie B. Newman's article, "Safety of Statins and Non-Statins for Treatment of Dyslipidemia," in this issue), and in 2015, the FDA removed the indication for the use of niacin in combination with a statin.

PCSK9 Inhibitor

Human proprotein convertase subtilisin/kexin type 9 (PCSK9) is an enzyme responsible for degrading LDL receptors. Evolocumab is a human monoclonal immunoglobulin that binds to PCSK9 in the liver thereby increasing the availability of LDL receptors resulting in decreased serum LDL-C levels. In adult studies, evolocumab has been shown to decrease LDL-C levels up to 60%.[63] A recent study on the efficacy and safety of evolocumab added to statin therapy in children aged 10 to 17 years with heterozygous FH showed an average decrease of LDL-C levels of about 38% compared with placebo.[64] The most common adverse events were nasopharyngitis, headache, upper respiratory tract infection, influenza, oropharyngeal pain, and gastroenteritis; however, the incidence of adverse events was similar in the evolocumab and the placebo groups.[64] Evolocumab is given as a subcutaneous injection once a month at a dose of 420 mg; it is now approved by the FDA for children older than 10 years with heterozygous and homozygous FH.

Fibrates

Fibric acid derivatives, fenofibrate and gemfibrozil, lower serum TG levels by acting as agonists of the peroxisome proliferator-activated receptor alpha (PPARα) causing upregulation of lipoprotein lipase in adipose tissue and muscle leading to decreased TG levels. These derivatives are not approved by the FDA for use in pediatric patients but may be used in adolescents with a fasting TG level of greater than 500 mg/dL with an increased risk of pancreatitis. Most common side effects include nausea, vomiting, and abdominal pain.[56] Fibrates should not be used with statins due to an increased incidence of myositis, myalgia, and rhabdomyolysis and are contraindicated in patients with gallbladder disease.[65]

Omega-3 Fish Oils

Omega-3 fish oils contain eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) both of which lower TG levels by reducing circulating nonesterified fatty acids, the primary source of fatty acids for VLDL-TG production.[66] Evidence suggests that omega-3-fatty acids reduce apo-C III plasma levels via the PPARα pathway, decrease hepatic fatty acid and TG synthesis, and augment fatty acid degradation/oxidation, causing overall reduction in hepatic VLDL cholesterol synthesis and release. Omega-3 fish oil has been studied in the adult population and shown to reduce TG levels by 30% to 45% and increase HDL-C levels.[67] Adult studies show an increased reduction of TG levels with higher doses (4 g/d) compared with lower doses (1 g/d).[68] DHA has been shown to increase LDL-C levels and change LDL particle size, whereas both EPA and DHA lower TG levels and increase HDL-C levels.[69–71] Prescription fish oils have not been approved by the FDA for use in children; however, over-the-counter (OTC) preparations are commonly used in children to lower serum TG levels. OTC preparations may have varying amounts of EPA or DHA, whereas prescription fish oils contain specific amounts of these oils. Fish oils in adult studies have side effects including gastrointestinal upset and unpleasant taste or smell, and less frequently, atrial fibrillation.

CLINICS CARE POINTS

- Universal screening in all children aged 9 to 11 years and 17 to 21 year will aid in improving cardiovascular health of the US population.
- Targeted screening in children with high-risk factors, like diabetes mellitus, chronic renal disease, nephrotic syndrome or end-stage renal disease, Kawasaki disease, chronic inflammatory diseases, post–heart transplant, or human immunodeficiency virus, will significantly reduce their clinical CVD risk in adult life.
- Lifestyle modifications with heart-healthy diet and moderate-vigorous activity are fundamental in the management of pediatric dyslipidemia.
- Pharmacotherapy with statins, BASs, ezetimibe and PCSK9 inhibitors, fibrates, niacin, and omega-3 fish oils are available for use in the pediatric population.

DISCLOSURE

The authors have nothing to disclose.

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