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Review Article

Pediatric Dyslipidemias: Screening, Diagnosis and Management

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Received: January 23, 2020; **Published:** February 25, 2020

Abstract

Through the last 50 years, it has become evident that atherosclerosis begins in childhood. Even if cardiovascular disease (CVD) events are uncommon in children, studies have found the subclinical disease in association with measurable risk factors during childhood. Identifying this susceptible population makes the chance to prevent the development of risk factors and CVD events in the future with effective management of genetic and acquired risk factors. In the United States, approximately 20 percent of children (age 6 - 19 years) have adverse levels of one or more lipid values. Childhood dyslipidemia has a major genetic component, but environmental factors for example diet and lack of physical activity can also influence the lipid profile. Familial hypercholesterolemia (FH) is a genetic condition causing lifelong elevations in low-density lipoprotein cholesterol (LDL-C). Early detection and proper management of these patients are essential to reduce CVD morbidity and mortality. Pediatric dyslipidemia guidelines were first published in 1992, following by a gap during which no formal guidelines were developed. In 2011, the National Heart, Lung, and Blood Institute guidelines for CVD risk reduction in children were published. Besides screening individuals with a family history of hypercholesterolemia and/or premature CVD, the Expert Panel recommended universal screening of all children between 9 and 11 years, and that LDL-C levels should be below 110 mg/dL in children and adolescents. Statins are considered as first-line therapy owing to their proven efficacy to reduce LDL-C and improve other lipid parameters in children. They have also been shown to have a positive effect on atherosclerosis. Safety is of particular concern with children; however, studies have so far documented that the side-effect profile of statins in children is comparable to that in adults.

Keywords: *Pediatric Dyslipidemia; Low-Density Lipoprotein Cholesterol; Cardiovascular Disease; Management Guidelines; Statins*

Abbreviations

CVD: Cardiovascular Disease; FH: Familial Hypercholesterolemia; LDL-C: Low: Density Lipoprotein Cholesterol; NCEP: National Cholesterol Education Program; NHLBI: National Heart, Lung and Blood Institute; AHA: American Heart Association; AAP: American Academy of Pediatrics; HDL-C: High Density Lipoprotein Cholesterol; TC: Total Cholesterol; T2DM: Type 2 Diabetes Mellitus; BMI: Body Mass Index; RCTs: Randomized Controlled Trials; FDA: Food and Drug Administration

Introduction

In adults, dyslipidemia is an established risk factor for cardiovascular disease (CVD), and correction of dyslipidemia reduces the risk of CVD. Dyslipidemia often starts in childhood and adolescence. When present at a young age, CVD risk factors progress into middle age and have been linked with a moderate to high risk of CVD in the future [1]. Identifying children with dyslipidemia and successfully improving their lipid profile may decrease the risk of accelerated atherosclerosis and premature CVD. In 1992, the National Cholesterol Education Program (NCEP) published the first guidelines for lipid screening in children and adolescents [2]. However, these guidelines did produce

some controversy with concern about how clinically important dyslipidemia was for young patients. Additionally, there was concern regarding the potentially aggressive treatment of dyslipidemia in children with medication [3]. With further knowledge and experience, these guidelines have been revised to include other risk factors and related conditions that further accelerate the risk for future CVD [4]. The most recent guidelines for screening, evaluation, and treatment of dyslipidemia in children and adolescents were developed as part of a National Heart, Lung and Blood Institute (NHLBI) process to develop an evidence-based, integrated set of guidelines that would cover all risk factors for CVD in children [1]. The NHLBI guidelines are endorsed by the American Academy of Pediatrics (AAP) and the American Heart Association (AHA) [4,5]. Publication of the NHLBI guidelines has promoted a healthy debate, both pro and con, on how best to prevent CVD starting in youth. The definition of pediatric dyslipidemia, screening to identify children with lipid disorders, and interventions will be reviewed here.

Definition of pediatric dyslipidemia

After birth, levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein-cholesterol (HDL-C) increase for the first 2 years of life, followed by a plateau until adolescence. During puberty, the total and LDL-C levels fall to the extent of 10% to 20% or more [6]. Based on the normative data, cutoff points are used to define lipid values as "acceptable," “borderline" and "abnormal" (Table 1). These definitions are consistent with the statement of the NHLBI Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, the AAP policy statement and the AHA [1,4,6]. Nevertheless, it should be noted that these cut-off points have not been validated as accurate predictors for accelerated atherosclerosis or CVD events [7].

Category	**Acceptable (mg/dl)**	**Borderline (mg/dl)**	**High (mg/dl)**
TC	< 170	170 - 199	≥ 200
LDL-C	< 110	110 - 129	≥ 130
Non HDL-C	< 120	120 - 144	≥ 145
Triglycerides 0-9 y 10-19 y	 < 75 < 90	 75 - 99 90 - 129	 ≥ 100 ≥ 130
Category	**Acceptable**	**Borderline**	**Low**
HDL-C	> 45	45 - 40	< 40

Table 1: *Definition of lipid levels in children and adolescents from the 2011 Expert Panel Integrated Guidelines*

The threshold points for high and borderline-high values represent approximately the 95 and 75 percentiles, respectively. Low threshold points for HDL-C represent approximately the 10 percentile.

The etiology of pediatric dyslipidemia includes the following:

- Monogenic conditions due to a single gene defect, such as familial hypercholesterolemia (FH), familial defective apolipoprotein B and familial hypertriglyceridemia.
- Secondary dyslipidemia related to specific diseases, conditions, or exposures, such as obesity, hypothyroidism, nephrotic syndrome, type 2 diabetes mellitus (T2DM), alcohol or drugs.
- Polygenic defects (Idiopathic).

Screening

Risk factors associated with CVD have been shown to progress from childhood into adulthood. Screening for lipid disorders in childhood is based on the rationale that early identification and treatment of pediatric dyslipidemia will reduce the risk and severity of CVD in adult life [1,8]. Although practicing a healthy lifestyle at a young age is the best way to prevent premature CVD in individuals with no mutation in the LDL-C metabolic pathway, effective and safe interventions are there for the management of those at moderate to high risk, especially children with genetic dyslipidemia such as FH. Lipid disorders are clinically silent in the majority of cases, and selective screen-

ing alone (i.e. screening only children with a positive family history) fails to identify a large number of children with lipid disorders. Age 10 years (range 9 - 11 years old), therefore, appears to represent an ideal time for screening all children (i.e. universal screening).

Randomized controlled trials evaluating the long-term effectiveness of screening and treatment in childhood are lacking, and no data are available on the cost-effectiveness of lipid screening methods in the pediatric population. The evidence supporting the potential benefits of screening and treatment in children comes from short-term trials in high-risk populations and studies demonstrating links between pediatric dyslipidemia and atherosclerosis. Nevertheless, after a review of the existing literature, the 2011 United States NHLBI expert panel established guidelines that recommend screening all children for dyslipidemia [1]. These guidelines combine the two complementary approaches of universal screening before and after the onset of puberty and selective screening at other ages. The recommendation for universal screening is based, in part, on the likelihood of identifying and treating the greatest number of individuals with FH, a group at high risk for significant morbidity and early mortality [4].

Who should be screened

Two categories of screening have been identified [1]. The first, targeted screening, is recommended in any child after the age of 2 years in whom one or both parents are known to have hypercholesterolemia or are receiving lipid-lowering medications, who have a family history of premature CVD (men < 55 years old, women < 65 years) and who have a moderate to high risk for premature CVD. The second category (universal screening), is recommended for all children 9 to 11 years of age, irrespective of general health or the presence/absence of CV risk factors. Second screening should be performed between 17 - 21 years of age.

What to order

Either a fasting or non-fasting lipid panel can be ordered for screening. If the individual is fasting, a standard lipid panel can be used (TC, triglycerides, HDL-C, LDL-C). If the individual is not fasting, a non-HDL-C (TC-HDL-C) is recommended as the first screening test since it is not affected by food, which often raises triglyceride (TG) or TG dependent values such as a calculated LDL-C. Ingestion of food or beverages has a minimum effect on directly measured LDL-C and the calculated non-HDL-C. If the non- HDL-C is >145 mg/dL, two fasting lipid profiles should be obtained and the results averaged before determining the most suitable intervention. Recommended screening tests for secondary dyslipidemia are contained in table 2.

Condition	Screening tests
Hypothyroidism	Free T4, TSH
Liver diseases	CMP
Kidney diseases	CMP/UA
Diabetes mellitus	CMP/UA/fasting glucose/HbA1c
Obesity/insulin resistance	CMP/fasting glucose and insulin
Medications	Steroids, retinoids, oral contraceptives, protease inhibitors

Table 2: *Common secondary causes of dyslipidemia (modified from Ref. 9)*

CMP: Comprehensive Metabolic Panel (electrolytes, liver and renal function studies), HbA1c: Hemoglobin A1c; TSH: Thyroid-Stimulating Hormone; UA: Urinalysis.

Interpreting the results

Patients with "acceptable" values on lipid screening do not require any further evaluation. Values of concern and appropriate actions to take are shown in table 3.

Initial screening	Non-fasting	Fasting
LDL-C, mg/dL	_	> 130
Non-HDL-C, mg/dL	> 145	>145
HDL-C, mg/dL	< 40	< 40
Triglycerides, mg/dL <10 y old >10 y old	 _ _	 ≥100 ≥130
Action	Obtain a fasting lipid profile x2 Average results	Repeat the fasting lipid profile after 2 wk, but before 3 mo Average results

Table 3: *Interpreting the results of lipid screening in children (modified from Ref 1)*

Interventions

Instructions for an age-appropriate diet and tips for a healthy lifestyle should be provided for all children and their families, and in several cases, this will involve consultation with a registered dietitian. Whenever feasible, breast-feeding should be encouraged in all infants for the first 6 months of life. For children more than 2 years, the primary beverage should be fat-free, unflavored milk. Older children should be advised to drink water, avoiding sugar-sweetened beverages. The total fat content of the diet should be 25% to 30%, with < 10% saturated fats, up to 20% as mono- and polyunsaturated fats, while avoiding saturated and trans fats as much as possible. Dietary fiber (5g + age in years/day) should be taken and salt consumption should be limited.

Approach to therapy

An algorithm, comprising the average of the child's two LDL-C results and the presence or absence of moderate- to high-risk factors and conditions, is used to select patients who are appropriate for drug therapy (Table 4) [9]. Adolescents with LDL-C levels > 250 mg/dL and/or triglycerides > 500 mg/dL should be referred to a specialist. Besides, patients with lower LDL-C values with a significant family history of premature CVD and any child for whom drug treatment may be indicated (LDL-C > 160 mg/dL if > 10 years with accompanying risk factors or >190 mg/dL without risk factors) would likely benefit from referral [1].

Parameter	Moderate risk	High risk
BMI	≥ 95th - 96th percentile	≥ 97th percentile
BP	High BP without treatment	High BP with treatment
Smoker	---	Current smoker
HDL	HDL-C < 40 mg/dL	-
Conditions	Kawasaki disease with regressed coronary aneurysms	Kawasaki disease with current coronary aneurysms
	Chronic inflammatory diseases	Types 1 and 2 diabetes mellitus
	HIV infection	Post-orthotopic heart transplant
	Nephrotic syndrome	Chronic renal disease/end-stage renal disease/ postrenal transplant
Recommended action		
LDL-C130-189	No risk factors/negative family history	CHILD-2-LDL diet + TLC
LDL-C 130-159	2 high-risk factors or 1 high-risk factor + ≥2 moderate risk factors or CVD	CHILD-2-LDL diet + statin
LDL-C 160-189	1 high-risk factor or ≥2 moderate risk factors or positive family history	CHILD-2-LDL diet + statin
LDL-C ≥ 190	---	CHILD-2-LDL diet + statin

Table 4: *Treatment algorithm for children with LDL-C ≥130 mg/dL (modified from Ref. 9)*

CHILD-2: Cardiovascular Health Integrated Lifestyle Diet-2 (The CHILD-2 diet recommends: 25 - 30% of total calories from fat; < 7% from saturated fat; < 10% from monounsaturated fat; and avoiding trans-fat); HIV: Human Immunodeficiency Virus; TLC: Therapeutic Lifestyle Counseling.

Secondary causes of dyslipidemia should be excluded and, when possible, families should be referred to a dietitian for age-appropriate dietary instruction. Depending upon the type and severity of dyslipidemia, selected children may require specific recommendations for dietary strategies to reduce LDL-C or TGs [1].

Children who are overweight or obese also should be encouraged to achieve and maintain a healthy weight, and all children should be instructed in obesity prevention by adopting a healthy lifestyle, including 60 minutes/day of moderate to strenuous exercise. Therapeutic lifestyle changes are specifically important for children who do not yet meet diagnostic criteria for being overweight/obese but have crossed body mass index (BMI) percentiles.

Drug therapy for elevated LDL-C

When medical intervention is recommended to lower LDL-C, a statin is the drug of choice [1]. Overall, statin therapy is not recommended below the age of 10 years unless there is a significant family history of premature CV events, the child has ≥ 1 high-risk conditions, or the child has multiple risk factors. Treatment should start with the lowest available dose of a statin administered once daily. All statins, except pitavastatin, have been approved by the US Food and Drug Administration (FDA) for use in children with FH; pravastatin at 8 years and older, all others (simvastatin, fluvastatin, lovastatin, atorvastatin, and rosuvastatin) at 10 years and older. Table 5 provides an overview of the statins currently approved by the FDA for children [10].

Statin	Licensed indication in children and adolescents	Preparation	The recommended dose in children
Atorvastatin	10 - 17 years with FH	Tablet	10 - 20 mg/day
Rosuvastatin	10 - 17 years with FH	Tablet	5 - 20 mg/day
Simvastatin	10 - 17 years with FH	Dissolvable tablet	10 - 40 mg/day
Lovastatin	10 - 17 years with FH	Extended-release tablet	10 - 40 mg/day
Fluvastatin	10 - 16 years with FH	Capsule	20 mg/day
Pravastatin	> 8 years with FH	Tablet	8 - 13 years: 20 mg/day 14 - 18 years: 40 mg/day
Pitavastatin	Not currently licensed in children or adolescents	Extended-release tablet	NA

Table 5: *FDA-approved statins (modified from Ref. 10)*

In children with elevated LDL-C, genotype confirmation provides unequivocal evidence of FH and supports the need for early medical treatment [1]. Although high LDL-C values are also found in polygenic dyslipidemias (e.g. familial combined hyperlipidemia), genotyping usually is not recommended in these cases. Individuals with dyslipidemia secondary to polygenic disorders also can get benefit from early medical treatment, though the evidence for treatment efficacy has largely been based on studies in genotype-confirmed monogenic hypercholesterolemia (e.g. FH). The treatment goal is to attain an LDL-C < 130 mg/dL, ideally < 110 mg/Dl [1]. If the desired target is not achieved, then the dose of statin may be increased by one increment (generally 10 mg), and liver function tests should be repeated in 4 weeks. If the LDL-C level remains above the target, the statin dose may be further increased by one increment. However, it should be kept in mind that each doubling of the statin dose only results in approximately a 6% reduction in LDL-C. If lifestyle modifications combined with a statin are unsuccessful, adding other lipid-lowering medications can be considered [1]. Ezetimibe, a cholesterol-absorption inhibitor, and colesevelam, a bile-acid sequestrant, are FDA approved to lower LDL-C in children ≥10 years with FH. Proprotein convertase subtilisin/kexin type 9 (PCSK 9) inhibitors have emerged as a most promising approach for treating severe hypercholesterolemia, including FH. Despite many published studies with these drugs, there are very few data concerning their effects on pediatric patients with FH. Other LDL lowering therapies like Mipomersen, Lomitapide, and LDL apheresis, have very little evidence in the pediatric population.

Drug therapy for elevated triglycerides

Children with TG levels > 500 mg/dL are at risk for pancreatitis. Although there are no FDA-approved medications to prevent pancreatitis in youth < 18 years with a markedly raised TG level (> 500 mg/dL), the NHLBI Expert Panel suggested fibric acid derivatives, and omega-3 fatty acids could be considered in consultation with a specialist [1]. These agents mainly influence hepatic TG production. The markedly elevated TG levels in familial hyperchylomicronemia, however, are caused primarily by dietary-derived chylomicrons, which cannot be removed from the circulation in the absence of effective lipoprotein lipase activity [11]. There is information supporting the use of pre-prandial orlistat, a pancreatic lipase inhibitor, along with a very low-fat diet for preventing pancreatitis in children with familial lipoprotein lipase deficiency [12]. The addition of omega-3 fatty acids to reduce modestly elevated TG levels can also be considered a potential treatment, although it is not yet approved for children. The effective dose has not been established.

Drug therapy for mixed dyslipidemia

Although a major focus of the 2011NHLBI guidelines is the detection and treatment of children with elevated LDL-C, especially FH and FCH, the commonest dyslipidemia encountered in clinical practice is an elevated TG combined with a low HDL-C [1]. Even though this pattern of ''atherogenic dyslipidemia'' can be genetic, it is most commonly seen in children who are obese (body mass index ≥ 95th percentile) and insulin-resistant (clinically manifest by the presence of acanthosis nigricans, prediabetes, hypertension; and in girls, polycystic ovary syndrome). It is, however, important to note that obesity can exacerbate underlying genetic dyslipidemia and thereby accelerate the atherosclerosis process. The safest and most effective treatment for acquired dyslipidemia is lifestyle modification, encouraging healthy eating habits, moderate to strenuous daily physical activity, and achieving a healthier body weight (e.g. in most cases, 5% - 10% reduction in body weight). Avoiding the adverse consequences of smoking is particularly important in youth with CVD risk factors or conditions. Currently, no medical interventions are approved in children with a low HDL-C, other than alleviating the standard CVD risk factors with lifestyle changes.

Monitoring

Table 6 lists the recommended monitoring of children following initiation of statin therapy. The child's risk factors and family history should be updated frequently.

Statin therapy	1st year				2nd year	Targets
	Baseline	1 mo	2 mo	Every 3 - 4 mo	Every 6 mo	
Laboratory monitoring						
Lipid profile	√	√	√	√		LDL-C
ALT	√	√	√	√		< 3 times ULN
AST	√	√	√	√		< 3 times ULN
CK	√	√				< 10 times ULN
Physical examination	√	√	√	√	√	
Height	√	√	√	√	√	Assess other factors (weight gain, smoking, physical inactivity) regularly
Weight	√	√	√	√	√	
BMI	√	√	√	√	√	
BP	√	√	√	√	√	
Sexual maturation Medication Monitoring						
Compliance	√	√	√	√	√	Advice about potential medication interactions; advise women and girls about concerns about pregnancy and need for appropriate contraception
Tolerance	√	√	√	√	√	
Adverse effects	√	√	√	√	√	

Table 6: *Recommended monitoring (modified from Ref 1)*

If laboratory abnormalities are noted or symptoms are reported, temporarily withhold medication and repeat blood work in 2 weeks. When abnormalities resolve, medication may be restarted, with close monitoring. ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; CK: Creatine Kinase; ULN: The Upper Limit of Normal

Concerns and controversy

The modern practice of medicine is directed, whenever possible, by published evidence to ensure efficacy while avoiding the potential for harm. In the absence of published evidence, practitioners, in general, rely on consensus opinions from experts in the field. The NHLBI selected a highly qualified panel of eminent experts who carefully and systematically examined the available evidence relevant to CV health and risk reduction in children and adolescents. Although RCTs were included in the Expert Panel reviews, particularly absent were the results of long-term RCTs of safety and efficacy. The latter is challenging in children because such trials take a long time to complete. Given the considerable benefit of statins in reducing CVD-related mortality in adults, withholding effective treatment in moderate- to high-risk children would be concerning to many healthcare providers [13,14]. Knowing these constraints, the Expert Panel extensively reviewed epidemiological, observational, and case-control studies in formulating its recommendations for youth. Only time and continued surveillance of the pediatric population at risk will let us know whether these recommendations are flawed. Considering the serious consequences of unrecognized or inadequately managed CVD risk factors as well as the known safety profile of statins in children, such recommendations seem warranted.

Benefits and harms

Recommendations for any screening program should depend on the assessment of benefits and harms and whether there are overall health gains. The screening of children for dyslipidemia appears justified by the benefits of offsetting early atherosclerosis [15] and preventing death [14]. This has been best established for FH with documentation of safety and minimal harms of statin treatment after age 8 [16] and dietary intervention in 8- to 10-year-olds [17]. Nevertheless, data on the effect of statins on coronary atherosclerosis in children are currently limited. Although long-term data are absent, cost-effectiveness for FH screening has been documented in the Netherlands [1] and screening family members of a proband was shown to be effective in the United Kingdom by increasing the detection rate and cost savings in long-term health [19]. The USPSTF review found no evidence of harm arises from lipid screening, but more long-term studies are required [20]. There were no psychosocial effects in 8- to 10-year-old children during subsequent dietary treatment for hypercholesterolemia in the well-powered Dietary Intervention Study in Children [16]. Measures should be taken to ensure a balanced dietary intake [1,21].

Statin Safety

Cholesterol is a vital component of cell membranes and serves as a precursor in the biosynthesis of steroid hormones. Therefore, it is important in the growth and development of children, including neurological development [10]. Justifiably then, there is a need to assess the long-term adverse effects of statins in children. In clinical studies, reports of adverse events in children and adolescents receiving statin treatment have been comparable to those reported for placebo [22]. Muscle and liver adverse effects are recognized as potential side effects of statin therapy and so need to be monitored along with other recognized side effects. Importantly, in studies of statins in children, changes in liver transaminase values and creatine kinase values and the incidence of rhabdomyolysis appear to be similar to those reported in adults [22]. Myopathy and changes in hepatic function require appropriate guidelines and evidence-based management. Concerns that the effect of statins on decreasing cholesterol synthesis may affect brain development or function seem to be baseless according to results of the pediatric and adult trials and absence of effects in children with homozygous FH who usually begin statin treatment at age 2 years. Numerous studies investigating the efficacy of statins in FH also reported on the effect of statin therapy on sexual maturation. However, these studies failed to find a significant impact on the sexual maturation of adolescents treated with statins [23,24]. Longer follow-up is required to fully explore any long-term effects on growth and sexual maturation. Only one study to date has assessed the safety of statins for over 10 years. Laboratory parameters were similar between FH patients and their unaffected siblings, and there were no obvious differences in growth, maturation, or educational level [25]. Cross-reactions with drugs metabolized in common with statin pathways should be avoided and prescribing for sexually active girls should be done along with pregnancy counseling and precautions.

Conclusion

Growing evidence suggests that childhood is a critical window in atherosclerosis development. Pediatric dyslipidemia contributes to early atherosclerosis, and by extrapolation to premature CVD. Screening helps to identify children with dyslipidemia, enabling them to start an effective management program early to prevent future CVD morbidity and mortality. The current pediatric dyslipidemia guide-

lines represent the best evaluation and synthesis of evidence available. Given the impact of premature CVD on the well-being of future generations and its cost to society, it is essential that such guidelines be understood and consistently implemented by primary care providers. Doing so will create the opportunity of improving future recommendations. In the absence of high-quality RCT data, clinicians should make the best use of the available evidence to make reasonable inferences that can inform decision making for their patients and their families. Statins have long been used in the management of dyslipidemia in adults, and several have been approved by the FDA for use in children with FH. Existing data suggest that the safety profiles of statins are comparable for children and adults; nevertheless, long-term studies will help verify this. The results of trials with PCSK9 inhibitors in pediatric patients are awaited. Because this is such an important area from a clinical standpoint, the evidence continues to build up and guidelines should undergo a process of re-evaluation.

Conflict of Interest

None to declare.

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Volume 4 Issue 3 March 2020