

Hyperlipidemia

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Practice Gaps

1. The US Preventive Services Task Force recently gave screening an "I," which is insufficient evidence for recommending universal screening for hyperlipidemia in children.
2. Pediatricians need guidance on causes, screening, and treatment options in the era of a childhood obesity epidemic.
3. Pediatricians need to be aware of the latest recommendation on screening tests, treatment, prevention, and dietary counseling.

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ABBREVIATIONS

AAP	American Academy of Pediatrics
apo	apolipoprotein
CAD	coronary artery disease
CVD	cardiovascular disease
FCHL	familial combined hyperlipidemia
FDA	Food and Drug Administration
FH	familial hypercholesterolemia
HDL	high-density lipoprotein
HDL-C	high-density lipoprotein cholesterol
HeFH	heterozygous familial hypercholesterolemia
HoFH	homozygous familial hypercholesterolemia
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
LPL	lipoprotein lipase
NHLBI	National Heart, Lung, and Blood Institute
TG	triglyceride
USPSTF	United States Preventive Services Task Force
VLDL	very low-density lipoprotein
VLDL-C	very low-density lipoprotein cholesterol

Objectives

 After completing this article, readers should be able to:

1. Understand the epidemiology and pathogenesis of hyperlipidemia in the United States and the current evidence relating to various screening tests, when to initiate treatment, and how to treat children with or without familial hypercholesterolemia.
2. Understand the importance of appropriate screening tests for hyperlipidemia, when to screen, and how to evaluate patients with a positive screen.
3. Describe nutritional, lifestyle, and pharmacologic treatments for hyperlipidemia and indications for each.
4. Describe how to provide nutritional counseling for hyperlipidemia, specifically foods to avoid and alternative options.

Abstract

Cardiovascular disease remains the top cause of morbidity and mortality in the United States. Atherosclerotic plaques are known to start in adolescence, and, therefore, young adults can be affected by coronary artery disease. Children with known risk factors, such as genetic predisposition, including familial hyperlipidemias, diabetes, and renal diseases, are at higher risk. With childhood obesity becoming an epidemic in certain parts of the United States, this problem is further highlighted as an important issue affecting children's health. There are unclear

recommendations for pediatricians regarding cholesterol screening of pediatric populations, when to initiate hyperlipidemia treatment with statin therapy, and when to refer to a specialist for further management. This article reviews the epidemiology and pathophysiology of hyperlipidemia, recommendations for screening and types of screening, management (including pharmacology), prognosis, and prevention.

EPIDEMIOLOGY

Cardiovascular disease (CVD) is the number one cause of death in the United States. In fact, 38% of adults affected by CVD have risk factors such as elevated serum lipid levels, diabetes, and high blood pressure. (1)

It is well-known that atherosclerosis starts at a young age, and the number of young individuals developing atherosclerosis is on the rise, especially children with risk factors such as familial hypercholesterolemia (FH), type 1 diabetes mellitus, and hypertension. In the past few decades, hyperlipidemia in children and adolescents has been increasing, and the American Heart Association identifies these children as being at higher risk for premature atherosclerosis. (2) Currently, 13% of adolescents have increased cholesterol levels, up from 10% between 1988 and 1994. (3)

FH is an autosomal condition due to mutations in the low-density lipoprotein (LDL) receptor gene, and it occurs in 1 in 274 to 1 in 500 individuals. (3)(4)(5)(6)(7)(8) In one study, one-third of patients with FH had 1 of the 48 mutations that are associated with this condition. (5) FH is further classified into 2 types, namely, homozygous (HoFH) and heterozygous (HeFH), with incidences of 1 in 160,000 and 1 in 200 to 1 in 500, respectively. (4) Patients with FH have an elevated plasma LDL cholesterol (LDL-C) level (≥ 140 mg/dL [≥ 3.6 mmol/L]) throughout life and an increased risk of cardiovascular events, including stroke and heart attack. In these patients, atherosclerosis can start as early as 10 years of age and will need treatment with statins to prevent progression. The incidence of coronary artery disease (CAD) is low during childhood in patients with HeFH, but the risk of early CVD and early events is increased 100-fold by 50 years of age in 50% of men and 25% of women if left untreated. (4)(9) Familial combined hyperlipidemia (FCHL) is one of the genetic causes of hyperlipidemia; it is reported to be 3 times more prevalent than FH and occurs in 0.50% to 1% of the population. (7)

In US children and adolescents aged 12 to 19 years, the prevalence of hypertriglyceridemia (triglyceride [TG] level >150 mg/dL [>1.7 mmol/L]) is approximately 10.7%,

mostly from secondary causes, such as obesity, types 1 and 2 diabetes, medications, and renal and liver disease; less than 0.2% have severe hypertriglyceridemia (TG level >500 mg/dL [>5.7 mmol/L]). (7) Causes of primary hypertriglyceridemia include lipoprotein lipase (LPL) deficiency, which has an incidence of 1 in 500,000 to 1 in 1,000,000, and dysbetalipoproteinemia, which has an incidence of 1 in 5,000. (7) Type V hyperlipoproteinemia is rare and accounts for 5% of patients with hypertriglyceridemia. (10)

PATHOGENESIS

Hyperlipidemia is characterized by elevated levels of lipids that can be caused by a variety of genetic or acquired disorders. In adults, hyperlipidemia has been shown to be a major risk factor in developing CVD. Studies have shown that atherosclerotic processes develop early in childhood, with fatty streaks reported in the aortas and coronary arteries of patients as young as 10 years old. (11)

Overview of Lipid Metabolism

Disruption of lipid metabolism is common to all types of pediatric dyslipidemias. The use of lipids as an energy source begins with the ingestion of dietary fats, which are broken down by bile acids and absorbed by the intestinal lumen. In the intestinal cell, free fatty acids are combined with a glycerol molecule to form TGs, and cholesterol is made into a cholesterol ester by the enzyme acyl-coenzyme A: cholesterol acyltransferase. The TGs and cholesterol esters are then combined with apolipoprotein (apo)B-48 to form chylomicrons. The chylomicrons enter the systemic circulation through the lymphatic system and acquire apoC-II and apoE from high-density lipoprotein (HDL), which is first synthesized in the liver or the intestines from chylomicron and very LDL (VLDL) remnants. The chylomicron then binds to LPL, a receptor found on endothelial cells, to hydrolyze core TGs and deposit fatty acids in peripheral tissues as a source of energy.

In addition, TGs and cholesterol esters are synthesized endogenously to form VLDL, which binds to LDL receptors via surface apoB-100 and apoE and uses LPL for conversion to intermediate-density lipoprotein. The liver then modifies intermediate-density lipoprotein to become LDL, which functions to transport hepatic cholesterol to target cells via receptor-mediated endocytosis (apoB/E receptor) for possible hormone or steroid synthesis and/or improving cell membrane integrity. (12) LDL-C can also be oxidized, making it capable of being endocytosed through the scavenger receptor, creating foam cells, which have been shown to contribute to the formation of atherosclerotic plaques. (13)

Definition and Classification of Hyperlipidemia

The existence of hyperlipidemia in children is determined by LDL-C levels; specifically, LDL-C levels of 130 mg/dL or greater (≥ 3.4 mmol/L) meet the criteria for hyperlipidemia (Table 1). Hyperlipidemia in children can be divided into 2 categories: primary and secondary. Primary causes of increased TG levels include genetic defects in lipid synthesis and metabolism, and secondary causes are a result of medical conditions such as poorly controlled diabetes, nephrotic syndrome, obesity, and hepatitis. Primary causes can be divided into 4 different disorders: LPL deficiency, FCHL, familial hypertriglyceridemia, and dysbetalipoproteinemia (Table 2).

LPL deficiency is a rare autosomal recessive disorder that is characterized by a mutation in the *LPL* gene. Chylomicron and VLDL-C levels in the blood are increased due to inability to

hydrolyze their TG cores. Accumulation of chylomicrons in internal organs leads to organ enlargement and inflammatory changes to the pancreas, which if not properly treated may present as recurrent abdominal pain and pancreatitis. (14) Homozygous and compound heterozygous carriers have absent or significantly reduced LPL levels, whereas heterozygous carriers could have normal levels of LPL and be asymptomatic. Hyperchylomicronemia can also be seen with mutations in apoC-II and glycosylphosphatidylinositol-anchored HDL-binding protein, a protein responsible for the exposure of LPL on endothelial cell surfaces. (7)

FCHL is a complex genetic disorder with a prevalence of 0.5% to 1% of the population. Although not completely understood, FCHL is characterized by an overproduction of VLDL-C and apoB-100 in the liver, a reduction in fatty acid uptake by adipose tissue, and decreased clearance of chylomicrons. The resulting lipid panel for these patients may show increased LDL-C and TG levels with decreased HDL-C levels. Pediatric patients do not typically present with symptoms, but weight gain in adolescents may make the diagnosis apparent. (15)

Familial hypertriglyceridemia is an autosomal dominant disorder that presents similarly to FCHL. This condition also involves overproduction of VLDL-C by the liver and decreased catabolism of TGs; however, unlike FCHL, familial hypertriglyceridemia does not have increased production of apoB-100. Because of this, there is no increase in LDL-C levels, and lipid panels would show TG levels of 250 to 1,000 mg/dL (2.8–11.3 mmol/L) and low to normal HDL-C levels. (16)

TABLE 1. Lipid Cutoff Levels for Pediatric Patients Established by the 2011 Expert Panel Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents

LIPID	CUTOFF LEVEL		
	CATEGORY, mg/dL (mmol/L)	BORDERLINE	HIGH/LOW
Total cholesterol	<170 (<4.4)	170–199 (4.4–5.1)	≥ 200 (≥ 5.2)
LDL-C	<110 (<2.8)	110–129 (2.8–3.3)	≥ 130 (≥ 3.4)
Non-LDL-C	<120 (<3.1)	120–144 (3.1–3.7)	≥ 145 (≥ 3.8)
Apolipoprotein B	<90 (<2.3)	90–109 (2.3–2.8)	≥ 110 (≥ 2.9)
Triglycerides			
Age 0–9 y	<75 (<0.85)	75–99 (0.85–1.12)	≥ 100 (≥ 1.13)
Age 10–19 y	<90 (<1.02)	90–129 (1.02–1.46)	≥ 130 (≥ 1.47)
HDL-C	>45 (>1.2)	40–45 (1.0–1.2)	<40 (<1.0)
Apolipoprotein A-1	>120 (>3.1)	115–120 (3.0–3.1)	<115 (<3.0)

HDL-C=high-density lipoprotein cholesterol, LDL-C=low-density lipoprotein cholesterol.

TABLE 2. Types of Hyperlipidemia and Key Features

TYPE	INCIDENCE	PRESENTATION	TREATMENT
Heterozygous familial hypercholesterolemia	1 in 200 to 1 in 500	Asymptomatic	Diet and exercise for 6 mo, add statins
Homozygous familial hypercholesterolemia	1 in 160,000	Xanthomas	Diet, exercise and statins, bile acids, cholesterol absorption inhibitors
Primary hypertriglyceridemia	<0.2%	Identified by pancreatitis	Fibrates Nicotinic acid Plasmapheresis
Secondary hypertriglyceridemia	10.7%	Other secondary diagnosis, such as diabetes, renal dysfunction	Fibrates Nicotinic acid Omega fatty acids
Familial combined hyperlipidemia	0.5%–1%	May be obese	Diet, exercise, statins

Finally, dysbetalipoproteinemia is a disorder with a homozygous mutation in apoE that binds chylomicrons, intermediate-density lipoprotein, and VLDL to the surface of hepatocytes. This leads to increased levels of chylomicron and VLDL remnants as well as an increase in TG and total cholesterol levels. Palmar crease xanthomas have been shown to be pathognomonic in the pediatric population. Although LDL-C levels and apoB levels are low, patients with dysbetalipoproteinemia have an elevated risk of CVD; elevated levels of β -VLDL have a powerful action on monocyte-macrophage cells and rapidly transform these cells into foam cells activating the atherosclerosis pathway. (17) Compared with FH, dysbetalipoproteinemia can lead to earlier development of hypercholesterolemia, with resulting CAD, peripheral artery disease, and a great risk of developing glomerular nephritis and pancreatitis. (17)

MANAGEMENT

Management of hyperlipidemia should be centered around the underlying cause of elevated cholesterol levels. It should be determined whether patients have a primary cause for hyperlipidemia, such as FH, or whether the cause is incidental or secondary. (18)(19) It is important to monitor for the secondary causes of hyperlipidemia, namely, nephrotic syndrome, hypothyroidism, diabetes, cholangiolithic hepatitis, obesity, anorexia nervosa, diet-related (excessive intake of dairy products), or drug-induced (oral contraceptive pills, corticosteroids, cyclosporine, etc). (4)(7)(8)

Hyperlipidemia Screening

Routine screening of pediatric patients for elevated cholesterol levels remains controversial because it involves testing for a risk factor of atherosclerosis and not for the disease itself. (5)(20)(21)(22) Universal screening of the pediatric population

has previously been recommended by the American Academy of Pediatrics (AAP) based on recommendations from the National Heart, Lung, and Blood Institute (NHLBI). Some would recommend performing these screenings during health supervision visits when children receive their immunizations at regular intervals. (23) However, the US Preventive Services Task Force (USPSTF) in 2016 reported an “I” recommendation (not for or against universal screening) and concluded that there was insufficient evidence to make recommendations regarding benefits and harms of cholesterol screening in childhood. (20)(21) The USPSTF does recommend screening for obesity at 6 years of age (B recommendation), which would include evaluation of lipid panels and other laboratory values as discussed later herein. (20) A study found that 0.3% of 10,095 children tested had positive screening results. (5)

Universal Screening

The USPSTF has assigned an “I” (insufficient evidence) to recommend cholesterol screening, whereas the NHLBI and the AAP recommend screening patients at 9 to 11 years of age (B rating) (7)(22)(24)(25) and again at 17 to 21 years, with testing at other ages indicated for positive family history, high-level risk factors, or new high-risk medical conditions. (21)(26) Concerns exist that targeted approaches to cholesterol screening for those with CVD risk factors may miss some children and adolescents, but the USPSTF argues that the abnormal lipid levels used for screening are based on population distributions rather than on health outcomes. (8)(24) The USPSTF also recognizes that the long-term outcome of cholesterol-lowering medication has not been fully evaluated. (24)

Regarding targeted versus universal screening, a cost analysis using a simulated cohort of 4.1 million children from the National Health and Nutrition Examination Survey found that universal screening, rather than targeted screening based on

positive family history of hyperlipidemia, was more cost-effective and would identify more children with hyperlipidemia. (14) In a 2016 systematic review of universal cholesterol screening in childhood, limited evidence for clinical benefit was noted, but positive effects may be found in lifestyle changes in children with elevated cholesterol levels. (27) However, the cost associated with universal screening is estimated to be approximately \$50 million and would be difficult to implement in the current health system. Neither the NHLBI nor the USPSTF had evaluated the cost-effectiveness of the recommendations. (8)(22)

Targeted Screening

Cholesterol screening based on risk factors is suggested for children 2 to 10 years of age with a positive family history of dyslipidemia or premature CVD in male relatives younger than 55 years and female relatives younger than 65 years, unknown family history, risk factors for CVD (overweight [BMI \geq 85th percentile or $<$ 95th percentile], obesity [BMI \geq 95th percentile], hypertension [blood pressure \geq 95th percentile], cigarette smoking, diabetes mellitus), or medical conditions associated with lipoprotein abnormalities (organ transplant, systemic lupus erythematosus, nephrotic syndrome, protease inhibitor treatment). (2)(7)(28) CVD in a family member can be defined as parents, aunts, uncles, and/or grandparents with a history of heart attack, angina, coronary artery bypass graft, stent, angioplasty, stroke, or sudden cardiac death. (7) Primary hypertriglyceridemia may also be suspected in patients with a family history of pancreatitis in multiple family members. (28) Evaluation should include height and weight, blood pressure, pubertal status, laboratory evaluation of complete lipid profile, basic metabolic profile, serum creatinine, serum blood urea nitrogen, liver function tests, hemoglobin A_{1c}, thyrotropin, free T₄, and urinalysis. (8)(28) The monogenic hyperlipidemias typically manifest in infancy (type 1 hyperlipidemia or familial hyperchylomicronemia syndromes), but some, such as apoC-II, apoA5, and LMF1, can have onset in adolescence. Pubertal status plays a role due to the changes secondary to hormones and can manifest as hyperlipidemias in adolescents. The Framingham scoring system is used in adults, but no current scoring system has been validated for establishing CVD risk in the pediatric population. (8)

Cascade Screening

A screening cascade occurs when screening of 1 patient results in an abnormal laboratory value suggestive of a diagnosis that then requires screening of other family members for that same diagnosis. (29) The practice is more common outside the United States. (24) This process involves trained individuals who contact additional families for screening once an index case has been identified, and it requires a significant system-level change to implement this care process in the United States. (8) One study noted that

there is an opportunity for this type of screening in younger patients due to the frequent and regular visits for immunizations and health supervision visits. (29) Unfortunately, this type of screening has limited use in the United States because adults associated with an index case might not be able to be screened due to lack of universal health care.

Considerations for FH

Early diagnosis of FH is important to prevent and/or reduce the risk of CVD related to atherosclerosis. Guidelines recommend diagnosis of HeFH with LDL-C levels of 140 mg/dL or greater (\geq 3.6 mmol/L) and a family history of FH or premature CAD; whereas, HoFH is diagnosed with LDL-C levels of 500 mg/dL or greater (\geq 13.0 mmol/L) and suspected if 400 mg/dL or greater (\geq 10.4 mmol/L). (4)(7)(14) It is also recommended to test LDL-C if the total cholesterol level is greater than 330 mg/dL ($>$ 8.6 mmol/L) and/or there is a family history of FH or premature CAD.

Presence of xanthomas can be a presenting symptom for HoFH and should prompt clinicians to consider evaluation of LDL-C level and family history for FH. (4)(5)(8) Recommendation for treatment of LDL-C levels greater than 180 mg/dL ($>$ 4.7 mmol/L) initially includes lifestyle modification and first-line medication with a statin beginning at the lowest dose and increasing if necessary to an LDL-C target of less than 140 mg/dL ($<$ 3.6 mmol/L). (4)(7)(18)(19)(25) Because atherosclerosis is predicted to progress rapidly in these patients, a child of 10 years is the ideal age to begin screening and pharmacotherapy to slow progression. (30) These patients should have referral to a specialist to evaluate for CAD, aortic valve stenosis, supravalvular aortic stenosis, and thoracic/abdominal aortic aneurysms. Genetic testing is not widely used for identifying gene mutations, but it is the most specific method for diagnosis of FH. (8)

HoFH Management

HoFH is typically accompanied by LDL receptor dysfunction; therefore, the cholesterol-lowering mechanism of commonly used drugs depends on the functional activity of the LDL receptor. Target levels of LDL-C may not be reached, so a combination of therapies may need to be used. Lipoprotein apheresis may be required should lipid-lowering drugs prove ineffective. (7) Because patients with HoFH may present with CVD in childhood, it is important to evaluate for symptoms of ischemia. Classic symptoms of ischemia include angina, dyspnea on exertion, abnormal blood pressure, or signs of peripheral arterial disease. (6) Severe hypertriglyceridemia should be treated similarly to HoFH. (19)

Inpatient Management

Pancreatitis is a well-documented complication of severe hypertriglyceridemia occurring in 1% to 4% of patients with

pancreatitis, and mild to moderate elevation in serum TG levels are found in one-third of all patients with acute pancreatitis. (10) Severe hypertriglyceridemia with concentrations of TGs greater than 1,000 mg/dL (11.3 mmol/L) with abdominal pain/pancreatitis require hospital admission and aggressive medical management, which can include initiation of lipid-lowering medications in addition to intravenous insulin to facilitate clearance of TGs by activation of LPL. (28) Plasmapheresis is typically reserved for severe cases with additional findings of lactic acidosis, severe hypocalcemia, acute respiratory distress, and/or organ failure, where immediate reduction of serum TG levels is necessary. During hospitalization, possible causes of secondary hypertriglyceridemia, such as diabetes, medication adverse effects, poor diet or alcohol consumption, or other comorbidities, should be investigated. Patients can be discharged from the hospital when the TG level is less than 1,000 mg/dL (<11.3 mmol/L) or less than 500 mg/dL (<5.7 mmol/L) in monogenic hypertriglyceridemia. The patient should be tolerating a nonfat diet before discharge with a goal to increase to less than 10% to 15% of total calories from fat after discharge. (2)(9)

Outpatient Management

Lifestyle Modification. The first-line therapy for an elevated lipid profile remains recommending a healthy lifestyle, which includes dietary modification, improving body weight, avoiding tobacco smoking or, if smoking, beginning smoking cessation, and 30 to 60 minutes of daily physical activity with moderate to vigorous intensity. (7)(18)(19)(25) Although dietary modifications remain under debate, decreasing intake of total, saturated, and trans fats may have a lipid-lowering effect, particularly on TG levels, and is a current recommendation despite modest declines in LDL-C levels. (7)(8)(28) A dietitian may be helpful in making dietary adjustments needed to reduce LDL-C levels without compromising appropriate growth and development. (25) A 5% to 10% reduction in excess weight has been shown to be beneficial for reducing CVD risk in obesity. (25) For patients with hypertriglyceridemia, dietary fat should be restricted to less than 10% to 15%, with 30% to 40% of daily calories from protein and 50% to 60% from complex carbohydrates. The dietary fat restriction can be useful once TG levels decrease below 500 mg/dL (5.7 mmol/L). (28) A 6-month trial of intensive lifestyle modification with weight management and exercise using a comprehensive team has been suggested before medication use in patients with intermediate TG levels in the 150 to 499 mg/dL (1.7–5.6 mmol/L) range. (19) In addition to dietary modifications, physical activity may be useful in increasing HDL-C values but, more importantly, may assist with weight reduction. (25)

Pharmacologic Management

Statins. Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are the first-line drugs for the treatment of hyperlipidemia by helping to decrease LDL-C and TG levels and increase HDL-C levels in familial and severe hypercholesterolemia. (2)(7)(8)(28) Statins should be initiated at the minimum dose, and dosing should be adjusted to achieve a target LDL-C level of 140 mg/dL or less (≤ 3.6 mmol/L) by increasing the dose, changing to a more potent statin, or adding another lipid-lowering drug, such as ezetimibe and resins. (30) As recommended by the AAP and the American Heart Association, the earliest age at which statins can be initiated is 8 and 10 years, respectively, after failure of lifestyle modifications. (2)(4)(8)(28)

Statins have a similar safety profile as in adults, and adverse effects include headache, myalgias, hepatotoxicity, myopathy, and, rarely, rhabdomyolysis. (18)(25)(28)(31) Most commonly, patients may have elevation in aspartate aminotransferase/alanine aminotransferase levels, but this improves after cessation of the medication. (31) Statins are contraindicated in pregnancy due to potential as a teratogen, so appropriate contraceptive measures and/or counseling are required in adolescent females. (2)(8)(28)

Statins have been studied in large randomized controlled trials to reduce morbidity and mortality of coronary events in adults in the high-risk category, and some studies have shown reduction in LDL-C levels of 21% to 39% in pediatrics as well. (18)(31)(32) Higher doses of statins have also been studied, with their use resulting in a 38% to 50% reduction in LDL-C levels by some reports. (18) Although adverse effect profiles and efficiency have shown promise in short-term studies, there are no published studies on the long-term effect of statins on morbidity, mortality, and adverse effects in children, (18)(31)(32) including relationship to diabetes mellitus (22) and kidney disease. (33)

There is evidence for the use of statins in children with FH, and statins are recommended as treatment for both types of FH. Fluvastatin and pitavastatin have been studied in children and adolescents with FH. (34) A systematic review in 2017 of the FH literature found reductions in mean LDL-C concentrations at any time point in studies from 6 weeks to 2 years. (32)

Bile Acid Sequestrants (Resins). Bile acid sequestrants (resins) act to decrease LDL-C levels with primary use for familial or severe hypercholesterolemia. (2) The adverse effects are usually gastrointestinal, including bloating, abdominal discomfort, and constipation. (2) Resins are generally considered safe and are approved for patients older than 10 years of age. (2)(4) However, resins can interfere with absorption of fat-soluble vitamins and folic acid, so supplementation may be needed. (4)

Cholesterol Absorption Inhibitors. Cholesterol absorption inhibitors (ezetimibe) act to decrease LDL-C levels with primary use for familial or severe hypercholesterolemia. (2) Adverse effects include gastrointestinal symptoms, hepatotoxicity, and myopathy. It is approved in the United States and Europe for patients older than 10 years and in some studies to be effective in treating HeFH. (4)(6) However, it is often used as an adjunct to other medications and has not been fully evaluated as monotherapy. (2)(8)

Fibric Acids. Fibric acids (fenofibrate and gemfibrozil) are used to decrease LDL-C and TG levels and increase HDL-C levels in hypertriglyceridemia (TG levels >600–1,000 mg/dL [>6.8–11.3 mmol/L]). (2)(7)(10) There are limited data in children, but fibric acids seem to be generally well tolerated as monotherapy and may be used with caution when combining with a statin. (2) Fibrates are first-line pharmacologic agents for severe hypertriglyceridemia despite limited data for the pediatric population. (28)

Nicotinic Acid. Nicotinic acid (niacin) is used to decrease LDL-C and TG levels and increase HDL-C levels in familial or severe hypercholesterolemia. Common adverse effects are flushing, glucose intolerance, headaches, hepatotoxicity, and myopathy. It is not used frequently due to the potential for severe adverse effects. (2)(7)(28) Flushing, caused by release of prostaglandin E₂ in the skin, can be reduced by giving aspirin 15 to 30 minutes before taking the drug. (7) However, caution should be exercised in the use of aspirin to prevent Reye syndrome. (28) Niacin has not been fully studied in the pediatric population.

Omega-3 Fatty Acids. The long chain omega-3 fatty acids (fish oils) are used to lower TG levels so that they may be used in severe hypertriglyceridemia as an adjunct. These work by reducing hepatic secretion of VLDL-C and enhancing

chylomicron metabolism. (28) It is more effective in adults than in the pediatric population and is not suggested as a single therapy. (10)(28)

Monitoring. Patients should receive follow-up testing of serum aspartate aminotransferase, alanine aminotransferase, creatine kinase, and lipid levels 1 month after initiating therapy (Table 3). Once the dose is stable, testing should continue every 3 to 6 months while monitoring for adverse effects such as growth abnormalities or secondary sexual characteristics. On high-dose statins, fasting plasma glucose and/or glycated hemoglobin levels should be measured because statins have been found to increase the risk of new-onset diabetes in adults. (4)(8)(10)

PREVENTION

Hyperlipidemia prevention is the most rational approach in pediatrics due to the lack of pediatric-specific protocols and Food and Drug Administration (FDA)-approved TG-lowering drugs once hyperlipidemia has been diagnosed. (7)(35) The preventive approach should include behavioral changes and avoidance of fatty foods, promoting a healthy diet and physical activity.

Behavior is learned, so children need to be taught about avoidance of cigarette smoking (or cessation if already started) and adopting healthy lifestyle choices. Prevention of diabetes and obesity will help in preventing hyperlipidemia but is also important in deterring comorbid complications. Clinicians can help motivate at-risk patients and families to make behavioral changes together for promoting lasting lifestyle effects. When discussing diet, children should follow a diet that provides optimal nutrition for growth and development. This includes a diet with less than 20% to 25% of calories

TABLE 3. **Drugs Used to Treat Hyperlipidemia**

DRUG	MECHANISM	ADVERSE EFFECTS	MONITORING	SPECIAL CONSIDERATIONS
Statins	Block cholesterol synthesis	Myopathy	LFT, CK	Contraception in adolescent females as teratogenic
Bile acids	Bind with cholesterol	Diarrhea, constipation	None	Can reduce absorption of fat-soluble vitamins
Cholesterol absorption inhibitors	Block absorption	GI adverse effects, myopathy	None	Not approved in children but can be used if necessary
Fibrates	Decreasing production of VLDL and clearing triglycerides	GI adverse effects	None	Can cause muscle damage when used with statins
Nicotinic acid	Antilipolytic effect	Flushing, glucose intolerance, myopathy	LFT	Flushing can be reduced by giving aspirin 15–20 min before

CK=creatinine kinase, GI=gastrointestinal, LFT=liver function test, VLDL=very low-density lipoprotein.

from fat, less than 7% of calories from saturated fat, and less than 200 to 300 mg per day of cholesterol; avoidance of trans fat consumption; and encouraging high water-soluble dietary fiber intake. (35)(36)(37)

In addition to dietary recommendations, all children should have 30 to 120 minutes of moderate to intense physical activity daily, which promotes weight loss, improves insulin sensitivity, reduces free fatty acid release from adipose tissue, and enhances LPL, leading to better clearance of TGs. (35)(36)

PROGNOSIS

Evidence exists for a clear correlation between dyslipidemia and the onset and severity of atherosclerosis in children and adolescents. (38) The combined pattern of moderate to severe TG elevation, normal to mild LDL-C elevation, and reduced HDL-C seen in obesity, in addition to children with predominantly high LDL-C levels, have been shown to be associated with the incidence and progression of atherosclerotic lesions in children and adolescents verified by pathology and imaging studies. (38) In both children and adults, non-HDL-C seems to be more strongly related to persistent dyslipidemia and subsequent atherosclerosis than total cholesterol, LDL-C, or HDL-C independently. (38) Childhood lipid and lipoprotein results as predictors of future adult lipoprotein profiles are found to be most strongly correlated between late childhood and the third to fourth decades of life. (38)

Comprehensive screening to identify children with dyslipidemias that place them at increased risk for accelerated early atherosclerosis can be vitally important, especially for children with identified risk factors. Evidence suggests that risk factors in adolescence or young adulthood have greater predictive ability for subclinical atherosclerosis than those measured in adults. (21) Children with homozygous FH and type 1 diabetes mellitus are determined to be at highest risk for CAD before age 30 years. (2) Other conditions and factors demonstrated in youth that have a relationship to subclinical atherosclerosis in adulthood are obesity, hypertension, chronic kidney disease, and tobacco use. (21)(38)

FH results in lifelong elevated cholesterol levels, and the lifetime risk is approximately 90% for the development of coronary heart disease in individuals with this condition. (21) At any given LDL-C level, the presence of an FH gene will triple the likelihood of coronary heart disease, and the FH clinical phenotype denotes a 5-fold increase in the likelihood of premature events. (21)

A recent Cochrane Review on statin use in children with FH reports that endothelial dysfunction represents one of

the earliest stages of atherosclerosis, showing clear predictive value for future CVD. (32) In addition, increased carotid arterial wall intima-media thickness serves as a surrogate marker of atherosclerotic change and is a reliable indicator of clinical outcomes later in life. (32)

NHLBI guidelines support early identification and control of dyslipidemia throughout youth and into adulthood as a means to reduce clinical CVD risk beginning in young adulthood. (38) This is most critical for children with FH who have long-term significantly elevated LDL-C levels. The most recent USPSTF recommendation statement includes a need for further investigation of the atherosclerotic process as it relates to future events to allow for better-designed trials with intermediate end points informing the natural history of cardiac disease. (21)(24) More research is needed on long-term effects and potential benefits of statin use for the general pediatric population with hyperlipidemia.

Evidence/Article Summary

Hyperlipidemia has become an increasingly common problem in US children and adolescents, especially due to the childhood obesity epidemic. There is still controversy and debate over universal lipid screening versus targeted screening in children.

- The US Preventive Services Task Force has given an insufficient recommendation for universal screening of hyperlipidemia in children (Quality B). (8)(24)
- However, the National Heart, Lung, and Blood Institute strongly recommends universal screening for all children 9 to 11 years of age (B evidence) and again at 17 to 21 years of age, which is endorsed by the American Academy of Pediatrics (Quality B). (7)(22)(24)(25)
- Pediatricians can individualize lipid screening by identifying children at risk and targeting screening to those with a positive family history, high-risk factors, or comorbid medical conditions such as diabetes mellitus, nephrotic syndrome, obesity, and hepatitis (Quality C).
- Lifestyle modification of diet and exercise are first-line therapies for hyperlipidemia; however, patients with homozygous familial hypercholesterolemia will need statin therapy as additional management (Quality C). (7)(18)(19)(25)(31)(32)
- Some studies note that statin therapy is associated with increased costs and harmful effects and should not be used in the general pediatric population because risk of CVD in children is almost zero (Quality C). (19)
- Long-term effects of statins on children are unknown, and more research is needed (Quality D). (18)(31)(32)

References for this article are at <http://pedsinreview.aappublications.org/content/41/8/393>.

PIR Quiz

Individual CME quizzes are available via the blue CME link under the article title in the Table of Contents of any issue. To learn how to claim MOC points, go to: <http://www.aappublications.org/content/moc-credit>.

1. A 17-year-old boy is seen in the clinic for a sports preparticipation evaluation. You learn that many of his family members have “high cholesterol,” but he does not know anything more specific. Several of his family members have had recurrent episodes of pancreatitis. You perform targeted screening and obtain a lipid panel, which showed the following values: low-density lipoprotein cholesterol (LDL-C), 105 mg/dL (2.7 mmol/L) (acceptable: <110 mg/dL [<2.9 mmol/L]); apolipoprotein B, 70 mg/dL (1.8 mmol/L) (acceptable: <90 mg/dL [<2.3 mmol/L]); and triglycerides, 450 mg/dL (5.1 mmol/L) (acceptable: <90 mg/dL [<1.0 mmol/L]). This clinical presentation and the laboratory data are most consistent with which of the following diagnoses?
 - A. Dysbetalipoproteinemia.
 - B. Familial combined hyperlipidemia.
 - C. Familial hypertriglyceridemia.
 - D. Lipoprotein lipase deficiency.
 - E. Familial hypercholesterolemia.
2. You are evaluating a 9-year-old boy with abnormal lipid values (LDL-C level of 550 mg/dL [14.2 mmol/L]). His initial presentation included xanthomas around his knees and elbows, a systolic heart murmur heard best at the right upper sternal border, and intermittent chest pain. The patient has a strong family history of hypercholesterolemia. Genetic testing is ordered and is most likely to show which of the following genetic patterns of inheritance in this patient?
 - A. De novo mutation.
 - B. Heterozygous (autosomal recessive).
 - C. Homozygous (autosomal dominant).
 - D. X-linked recessive.
 - E. X-linked dominant.
3. An 11-year-old boy with familial hypercholesterolemia has failed lifestyle modification management, and his LDL-C level remains greater than 250 mg/dL (>6.5 mmol/L). In consultation with the child and his parents, the decision is made to initiate drug therapy. You counsel the family regarding statins as the preferred medication class you will prescribe and discuss statin adverse effects. Which of the following adverse effects could potentially be attributable to this class of medication?
 - A. Constipation.
 - B. Diarrhea.
 - C. Flushing.
 - D. Glucose intolerance.
 - E. Myopathy.
4. A 19-year-old woman is followed in a healthy lifestyles program for adolescents. At a follow-up visit she has a BMI greater than the 95th percentile, hypertension (blood pressure >95 th percentile), and acanthosis nigricans on physical examination. She denies smoking but is sexually active, with no consistent method of contraception. Her lipid profile continues to demonstrate elevated levels of LDL-C (200 mg/dL [5.2 mmol/L]) and triglycerides (350 mg/dL [4.0 mmol/L]). You decide to initiate drug therapy. Which of the following drug classes will require a negative pregnancy test result and a long-acting contraceptive method before initiation of treatment in this patient based on her history?
 - A. Bile acids.
 - B. Cholesterol absorption inhibitors.
 - C. Fibrates.
 - D. Nicotinic acid.
 - E. Statins.

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5. Your presentation to residents on their cardiology rotation includes specific recommendations for the prevention of hyperlipidemia in the pediatric population. These recommendations include making healthy lifestyle choices, especially for diet, and avoidance of cigarette smoking. For a diet that promotes optimal nutrition for growth and development, you recommend which of the following diet advice?
- A. Avoid trans fat consumption.
 - B. Consume 400 mg of cholesterol per day.
 - C. Consume less water-soluble dietary fiber.
 - D. Obtain less than 5% of their total calories from saturated fat.
 - E. Obtain more than 30% of their total calories from fat.