Clinical and laboratory assessment of cardiovascular risk in children: Guidelines for screening, evaluation, and treatment

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Abstract. The early lesions of atherosclerosis begin in childhood and are related to antecedent cardiovascular disease (CVD) risk factors. Environmental and genetic factors (eg, diet, obesity, exercise, and certain inherited dyslipidemias) influence progression of such lesions. Identification of youth at risk for atherosclerosis includes an integrated assessment of these predisposing factors. Treatment starts with a diet low in total and saturated fat and cholesterol, use of water-soluble fiber, plant stanols and plant sterols, weight control, and exercise. Drug therapy, for example, with inhibitors of hydroxymethylglutaryl-CoA reductase, bile acid sequestrants, and cholesterol absorption inhibitors, can be considered in those with a positive family history of premature CVD and low-density lipoprotein cholesterol >160 mg/dL after dietary and hygienic measures. Candidates for drug therapy often include those with familial hypercholesterolemia, familial combined hyperlipidemia, the metabolic syndrome, polycystic ovarian syndrome, type 1 diabetes, and the nephrotic syndrome. Such dietary and drug therapy appears safe and efficacious. Early identification and treatment of youth with CVD risk factors and dyslipidemia are likely to retard the atherosclerotic process. Optimal detection and treatment of high-risk children either from the general population or from families with premature CVD will require a comprehensive universal screening and evaluation program.

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Several longitudinal studies from the general population have found that early atherosclerotic lesions of fatty streaks and fibrous plaques in children, adolescents, and young adults who died from accidental deaths are significantly related to higher antecedent levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C), lower levels of high-density lipoprotein cholesterol (HDL-C), and to other cardiovascular disease (CVD) risk factors, such as obesity, higher blood pressure levels, and cigarette smoking.1,2 In the Bogalusa Heart Study, these effects of risk factors on coronary lesion severity were multiplicative rather than additive.2

Increased body mass index (BMI) in 15-year-old children from Muscatine is a significant longitudinal predictor of coronary artery calcium in young adult males (30% positive) and females (10% positive) at age 33 years.3 Baseline risk score from the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study, and its change with time, predicted both coronary artery calcium up to 15 years before its assessment in the Coronary Artery Risk Development in Young Adults (CARDIA) study,4 and carotid intima medial thickness (IMT) from adolescence through young adulthood in The Cardiovascular Risk in Young Finns Study.5 The Finnish study also found that
dyslipidemia in childhood characterized as elevated LDL-C and triglyceride (TG) levels (type IIb phenotype) predicted carotid IMT in adulthood, an independent effect exacerbated by the presence of CVD risk factors and the metabolic syndrome. In the Bogalusa Heart Study, both childhood obesity and LDL-C predicted IMT in young adults. Medical students at Johns Hopkins who had a TC level >207 mg/dL had five times the risk of developing CVD 40 years later than those students who had a TC level <172 mg/dL.

Studies have also been performed in high-risk youth selected by virtue of CVD in a parent, or because they have inherited a known metabolic disorder of lipoprotein metabolism that produces premature CVD. Half of the young progeny of men with premature CVD before 50 years of age had one of seven dyslipidemic profiles. Elevated levels of apolipoprotein (Apo) B in the presence of normal LDL-C (hyperapobetalipoproteinemia or hyper-ApoB) were prevalent in young offspring of adults with premature CVD and hyper-ApoB. In the Bogalusa Heart Study, levels of ApoB and ApoA-I, the major apolipoproteins of LDL and HDL, respectively, and the ratio of ApoB to ApoA-I in young offspring, were stronger predictors of premature coronary artery disease (CAD) in their parents than LDL-C and HDL-C levels.

Examples of inherited lipoprotein disorders that often present in youth at high risk of future CVD include familial hypercholesterolemia (FH), due to a defect in the LDL receptor, and familial combined hyperlipidemia (FCHL), the prototype for hepatic overproduction of very low-density lipoproteins (VLDL), which is often accompanied by insulin resistance and the dyslipidemic triad of hypertriglyceridemia (hyper-TG), increased small, dense LDL particles, and low HDL-C (see also Disorders of VLDL and LDL overproduction).

These studies, and others, clearly have implications for the prevention of CVD in the 21st century.

The National Cholesterol Education Program (NCEP) Expert Panel on Blood Cholesterol Levels in Childhood published recommendations. The National Cholesterol Education Program (NCEP) Expert Panel on Blood Cholesterol Levels in Childhood recommended a prudent diet low in saturated fat and cholesterol (Step I) for all healthy American children over the age of 2 years. Calories were to be sufficient to maintain normal growth and development.

Clearly, with the recent epidemic of obesity and metabolic syndrome in American youth, excess calories, not sufficient calories, are the issue. The prevalence of overweight children has increased substantially in recent decades, from 4.0% in the early 1970s to 17.5% in 2001 to 2004 in the 6- to 11-year-old age group, and from 6.1% to 17.0% in the same time frame among adolescents aged 12 to 19 years. Both lipid abnormalities and excess weight in children persist into adulthood, particularly in those with a BMI >95th percentile, with overweight adolescents having a 70% chance of becoming overweight adults.

The initial treatment of dyslipidemia in the affected child is dietary and hygienic. Most dyslipidemic children will require a more stringent (Step II) diet, along with other hygienic measures, such as regular aerobic exercise and weight control. The efficacy and safety of diets low in total fat, saturated fat, and cholesterol to lower LDL-C levels in youth have been demonstrated across the age spectrum of pediatrics, eg, from the age of 7 months to the age of 7 years, and from 7 to 11 years in the Special Turku Coronary Risk Factor Intervention Project (STRIP), and from the ages of 8 to 10 years throughout adolescence in the Dietary Intervention Study in Children (DISC).

The NCEP Pediatric Panel formalized the use of dietary and drug treatment in children, focused on elevated LDL-C levels, particularly in those with a positive family history of premature CVD. At that time, bile acid sequestrants were the recommended drugs of choice, and inhibitors of the rate-limiting enzyme of cholesterol biosynthesis, hydroxymethylglutaryl-CoA (HMG-CoA) reductase, ie, “the statins,” were not recommended for use in children. Since then, a number of studies demonstrated the efficacy and safety of LDL-lowering by statins in male and female adolescents with heterozygous FH, a conclusion supported by the results of a recent meta-analysis.

There is a clear need to address CVD risk factors in children and to update the NCEP Pediatric Panel’s recommendations. Guidelines based on a systematic evidence review for the screening, diagnosis, and management of dyslipidemia, as well as obesity, hypertension, and other risk factors in pediatric patients, are currently being developed by the National Heart, Lung and Blood Institute Pediatric Cardiovascular Risk Reduction Initiative. The American Heart Association recently published a scientific statement on cardiovascular risk reduction in high-risk pediatric patients and drug therapy of high-risk lipid abnormalities in children and adolescents. An extensive and systematic evidence review for the screening and treatment of lipid disorders in children and adolescents has been prepared for the US Preventive Services Task Force.

The present review focuses on the screening, evaluation, and treatment of dyslipidemia and other CVD risk factors in the pediatric age group.

Screening for dyslipidemia in youth

Two major approaches have been considered to detect dyslipidemia in youth, that is, screening in the general population or in a selected population. The extensive literature related to these two screening approaches has been recently reviewed.
Traditionally, screening for dyslipidemias is recommended in selected children because they have multiple CVD risk factors, or a family history of premature CVD and/or hypercholesterolemia. LDL-C has been the main focus of diagnosis and treatment. Less attention has been paid to HDL-C and TG levels. Now with the metabolic syndrome evident in the younger population, the focus of screening is likely to be expanded to include other factors, such as obesity, low HDL-C, non–HDL-C, elevated TG, increased small, dense LDL particles, glucose intolerance and insulin resistance, and higher blood pressure levels. Both the current and evolving concepts in screening and treatment of dyslipidemias in the young will now be discussed.

Who to screen

Selective screening: Current NCEP lipid screening criteria

The NCEP Pediatric Panel recommended that screening be performed in at-risk children and adolescents if one of the following conditions were present:

1. A lipoprotein profile in youth whose parents and/or grandparents required coronary artery bypass surgery or balloon angioplasty prior to age 55
2. A lipoprotein profile in those with a family history of myocardial infarction, angina pectoris, peripheral or cerebral vascular disease, or sudden death prior to age 55
3. A TC profile in those whose parents have high TC levels (>240 mg/dL); this might be usefully expanded to a lipoprotein profile in offspring of parents who have any dyslipidemia, involving elevated LDL-C, non–HDL-C, ApoB, TG, or low HDL-C
4. A lipoprotein profile if the parental/grandparental family history is not known, or the patient has two or more other risk factors for CAD, including obesity (BMI >30 kg/m²), hypertension, cigarette smoking, low HDL-C, physical inactivity, and diabetes mellitus; additional risk factors might be added, such as hyper-TG and insulin resistance, which often reflect the presence of the metabolic syndrome (see also The metabolic syndrome).

Universal screening

Universal lipid screening of all children is controversial. The advantages and disadvantages of universal screening will now be discussed briefly. What are some of the arguments in favor of universal screening? First, current screening recommendations based on family history of CVD or hypercholesterolemia will fail to detect substantial numbers (from 17% to 90%) of children who have elevated lipid levels.

Universal screening might be performed to detect those with undiagnosed heterozygous FH or more marked FCHL who will require more intensive treatment, including the possibility of drug therapy. In a recent meta-analysis of screening for FH in a primary care setting, use of TC detected 88%, 94%, and 96% of cases, with false-positive rates of 0.1%, 0.5%, and 1%, respectively. This approach might be combined with a case-finding strategy in relatives of patients with FH.

Children and adolescents affected with dyslipidemia and/or obesity and other CVD risk factors often come from families with similar problems. For example, relatives of hypercholesterolemic schoolchildren in Muscatine had greater coronary mortality than relatives of normocholesterolemic schoolchildren. Obesity in Muscatine children, especially when blood pressure was also elevated, identified families whose members were at increased risk of death from CVD. In the same population, relatives of schoolchildren with hyper-TG did not have increased CVD mortality. However, hyper-TG combined with elevated TC may increase risk for early CVD. Thus, universal lipid screening, combined with an assessment of obesity, high blood pressure, and other CVD risk factors can lead to detection of relatives from families at high risk for CVD and its associated morbidity and mortality.

It is clear that CVD risk factors cluster in childhood and persist into adulthood. Although it is known that offspring of parents with CVD generally have higher LDL-C and TG and lower HDL-C both in childhood and young adulthood, the majority of children with dyslipidemia and multiple risk factors will be missed by selective screening.

That each child and adolescent should ideally have an assessment of their plasma lipids and lipoproteins makes sense. Although there are practical problems (see the following), and no longitudinal studies are available to show that treatment starting in childhood decreases adult CVD, one might argue that universal screening seems all the more urgent, given the epidemic of obesity and the metabolic syndrome in American youth.

What are some of the concerns about universal lipid screening in childhood? Use of TC in childhood to predict TC or LDL-C levels in young adults sufficiently high to warrant treatment is often associated with less than optimal sensitivity, specificity, and predictive power of a positive test. For example, if one uses a lower TC cut point, ie, the 75th percentile (about 170 mg/dL) (Table 1), the sensitivity (proportion of affected subjects identified) is higher and the specificity (proportion of normal subjects identified as normal) is lower, as is the predictive value of a positive test. If one increases the cut point for TC to the 95th percentile (about 200 mg/dL) (Table 1), the sensitivity decreases (more children are missed who are destined to be “affected” as adults) but the predictive power of a positive test increases (more test results >200 mg/dL correspond to adults who will require treatment). When one uses quantitative traits such as TC or LDL-C for screening, there is no simple resolution of this problem. Use of high LDL-C (>130 mg/dL) rather than a high TC as a cut point improves sensitivity in those with low HDL-C and the predictive power of a positive test in those with high HDL-C.
A number of longitudinal studies have found that when the 75th percentile for TC in children is used as a screening cut point, about half the individuals who will require treatment as adults are identified by universal lipid screening. In one report, the sensitivity was much lower when screening occurred during adolescence, presumably reflecting the temporary shift of LDL-C to lower values during this period.

Another unresolved issue is whether the detection of elevated TC or LDL-C in children and young adults will predict those who are destined to manifest premature CVD. In the Princeton Lipid Research Clinics Prevalence program follow-up study of about 30 years, the number (n = 20) of CVD events was small; the sensitivity of childhood LDL-C for prediction of adult CVD was 10.5% and specificity was 81%. Use of a family history did not substantively improve these results. It is likely that use of obesity and other risk factors listed in Table 2 are present. One alternative to waist circumference might be a BMI of 95th and 5th percentiles, respectively. Non–high-density lipoprotein (HDL) cholesterol values from Bogalusa are equivalent to NCEP Pediatric Panel cut points for low-density lipoprotein (LDL) cholesterol.

Screening for the metabolic syndrome

The screening criteria of the NCEP mentioned here were not designed specifically for children with the metabolic syndrome, but did include screening those with two or more CAD risk factors, including obesity. There is some discussion whether the metabolic syndrome is a clinical entity, or simply the aggregation of multiple CVD risk factors. In the Bogalusa Heart Study, metabolic syndrome variables (ie, BMI, homeostasis model assessment of insulin resistance, ratio of TG to HDL-C, and mean arterial pressure) coexisted in terms not only of their levels in childhood and adulthood, but also of long-term rates of change. Obesity was of critical importance in the development of metabolic syndrome in this study, again emphasizing that the prevention of obesity (and the metabolic syndrome) begins in childhood. As well, childhood obesity and LDL-C predict carotid IMT in young adults.

Clearly, specific criteria to screen for multiple CVD risk factors need to be developed for the pediatric age group. There is no consensus regarding the definition of metabolic syndrome in youth. The definition of the metabolic syndrome for children ages 12 to 17 proposed by Cook and colleagues is one of several. An adolescent is considered to have the metabolic syndrome if three or more of the factors listed in Table 2 are present. One alternative to waist circumference might be a BMI >90% for age and gender. Although waist circumference and BMI in children are not routinely determined, recent data from the Bogalusa Heart Study indicate that both BMI and waist circumference values, when categorized by a threshold approach, independently predicted CAD risk factors.

What to measure

For selective screening, a lipoprotein profile after an overnight fast should be measured for screening youth with

$$\begin{array}{|c|c|c|}
\hline
\text{Category} & \text{Acceptable} & \text{Borderline} & \text{High} \\
\hline
\text{Total cholesterol} & <170 & 170–199 & \geq 200 \\
\text{LDL cholesterol} & <110 & 110–129 & \geq 130 \\
\text{Non-HDL cholesterol} & <123 & 123–143 & \geq 144 \\
\text{Apolipoprotein B} & <90 & 90–109 & \geq 110 \\
\text{Triglycerides} & <75 & 75–99 & \geq 100 \\
0–9 years & <90 & 90–129 & \geq 130 \\
10–19 years & <75 & 75–100 & \geq 100 \\
\hline
\text{HDL cholesterol} & >45 & 35–45 & <35 \\
\text{Apolipoprotein A-I} & >120 & 110–120 & <110 \\
\hline
\end{array}$$

*Values for plasma lipid and lipoprotein levels are from the National Cholesterol Education Program (NCEP) Expert Panel on Cholesterol Levels in Children. Non–high-density lipoprotein (HDL) cholesterol values from Bogalusa are equivalent to NCEP Pediatric Panel cut points for low-density lipoprotein (LDL) cholesterol.

†Cut points for a high or low value represent approximately the 95th and 5th percentiles, respectively.

Values for plasma apolipoprotein B and A-I are from the National Health and Nutrition Examination Survey III.
a positive family history of premature CVD or dyslipidemia, with obesity, with multiple CVD risk factors, including the metabolic syndrome, and for those suspected of having secondary dyslipidemia. Such a profile will include TC, TG, LDL-C, HDL-C, and non–HDL-C. Levels of lipoproteins are typically measured and expressed in terms of their cholesterol content. LDL-C is calculated from the Friedewald equation: \( \text{LDL-C} = \text{TC} - (\text{HDL-C} + \text{TG}/5) \). Total TG in the fasting state divided by 5 is used to estimate the levels of VLDL-C. If the TG is >400 mg/dL, this formula cannot be used and a direct LDL-C may be measured. If the patient is nonfasting, TC, HDL-C, and non–HDL-C levels can be measured.

ApoB and ApoA-I might also be determined using well-standardized immunochemical methods. Such measurements might provide additional useful information, particularly in youth with premature CAD in parents. Age-, gender-, and race-specific cut points for ApoB and ApoA-I, empirically derived from the National Health and Nutrition Education Survey (NHANES) sample are available, providing cut points that might be used to define elevated ApoB and low ApoA-I (Table 2). ApoB provides an assessment of the total number of ApoB-containing lipoprotein particles.

Non–HDL-C

Non–HDL-C is determined by subtracting HDL-C from TC and can be measured in plasma from nonfasting patients. Non–HDL-C reflects the amount of cholesterol carried by the “atherogenic” ApoB-containing lipoproteins (VLDL, intermediate density lipoprotein [IDL], LDL, and lipoprotein [Lp](a)). In adults, non-HDL appears to be a better independent predictor of CVD than LDL-C. In children, non–HDL-C is at least as good a predictor as LDL of future dyslipidemia in adulthood. Percentiles for non–HDL-C have been determined in children from the Bogalusa Heart Study (Table 1).

Advanced lipoprotein testing

Plasma levels of VLDL, LDL, and HDL subclasses have been determined in children and adolescents by nuclear magnetic resonance (NMR) spectroscopy or by vertical-spin density-gradient ultracentrifugation in research studies (see also The metabolic syndrome), but cut points derived from these methods for the diagnosis and treatment of dyslipidemia in youth are not currently available.

Summary

For universal screening, the simplest approach appears to be the measurement of TC, HDL-C, and non–HDL-C in nonfasting specimens. However, treatment algorithms in pediatrics are usually focused on fasting LDL-C. Hyper-TG is usually assessed as part of the dyslipidemic triad and is often elevated in obesity and the metabolic syndrome. Thus, in an ideal screening program, TC, TG, LDL-C, HDL-C, and non–HDL-C would be assessed by performing a lipoprotein profile in the fasting state.

When to sample for dyslipidemia

Lipoproteins are very low in cord blood at birth. During the next 2 years, lipids and lipoproteins increase until 2 years of age, after which time they are quite constant until adolescence. Ten years of age has been proposed as a good time to obtain a lipoprotein profile. The children are older, able to fast easier, values are predictive of future adult lipoprotein profiles, and adolescence has not yet set in. Because levels of TC and LDL-C may fall 10% to ≥20% during adolescence, it is preferable to screen children at risk for familial dyslipidemias before adolescence, between 2 and 10 years of age. Even in FH heterozygotes, there is a significant fall in the 1:1 ratio of affected to normal in adolescence. If sampling occurs during adolescence and results are abnormal, then they are likely to be even higher after adolescence. If results during adolescence are normal, then sampling will need to be repeated toward the end of adolescence (for girls, 16 years of age; and for boys, 18 years of age).

The complete phenotypic expression of some disorders, such as FCHL, can be delayed until adulthood, so continued evaluation of patients from high-risk families with FCHL should occur well into adulthood. However, elevated ApoB is the first expression of FCHL in adolescents and young adults. Age-related factors, such as increased BMI, contribute to the degree of dyslipidemia in such youth.

Definition of dyslipidemia

The cut points to define elevated levels of TC, LDL-C, ApoB, non–HDL-C, and TG and a low level of HDL-C and ApoA-I in children and adolescents are found in Table 1. Dyslipidemia is present if one or more of these lipid, lipoprotein, or apolipoprotein factors are abnormal. In off-spring of young progeny of men with premature CVD before 50 years of age, seven different dyslipidemic profiles were present (Table 3). Such results emphasize the importance of evaluating a lipoprotein profile in the fasting state.

Using data from three major population-based prospective cohort studies, TC, LDL-C, HDL-C, and TG lipoprotein variables in adolescence were classified according to NCEP cut points (Table 1) and age-, gender-, and race-specific NHANES cut points and compared for their ability to predict abnormal levels in adulthood. NCEP cut points (compared with NHANES cut points) were more strongly predictive of high TC, LDL-C, and TG levels in adults, but less predictive of low HDL-C. Continued use of the current NCEP cut points for TC, LDL-C, and TG levels in adolescents appears indicated; the cut point for HDL-C might be revised upward, perhaps to 40 mg/dL, to improve the sensitivity of this measurement to detect adult low HDL-C, and to make the cut point congruent with that used in adults.
Classification of lipid disorders

Lipid disorders can be caused by a single gene defect or by expression of several genes (oligogenic). These genetic defects lead to abnormal lipid and lipoprotein metabolism and constitute the primary lipoprotein disorders (see Metabolic disorders of dyslipidemia in youth). Secondary lipid disorders (Table 4) are the result of other disease states such as diabetes and hypothyroidism, or conditions such as obesity and the metabolic syndrome, or environmental factors such as a diet rich in saturated fats, a sedentary lifestyle, or certain drugs (Table 4). Because some of the “secondary” disorders, such as diabetes or the metabolic syndrome, can also be influenced by oligogenic factors, there clearly can be a strong interplay between environmental and genetic factors, leading to dyslipidemia. In secondary lipid disorders, the associated disorder should be treated first in an attempt to normalize lipoprotein levels; however, the patient should be assessed for all CVD risk factors and managed accordingly.

Table 4 Causes of secondary dyslipidemia in children and adolescents

<table>
<thead>
<tr>
<th>Exogenous</th>
<th>Storage disease</th>
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<tbody>
<tr>
<td>Alcohol</td>
<td>Cystine storage disease</td>
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<tr>
<td>Oral contraceptives</td>
<td>Gaucher disease</td>
</tr>
<tr>
<td>Prednisone</td>
<td>Glycogen storage disease</td>
</tr>
<tr>
<td>Anabolic steroids</td>
<td>Juvenile Tay-Sachs disease</td>
</tr>
<tr>
<td>13-cis-retinoic acid</td>
<td>Niemann-Pick disease</td>
</tr>
<tr>
<td>Endocrine and metabolic</td>
<td>Tay-Sachs disease</td>
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<tr>
<td>Acute intermittent porphyria</td>
<td>Acute and transient</td>
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<tr>
<td>Type 1 and type 2 diabetes</td>
<td>Burns</td>
</tr>
<tr>
<td>Hypopituitarism</td>
<td>Hepatitis</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Others</td>
</tr>
<tr>
<td>Lipodystrophy</td>
<td>Anorexia nervosa</td>
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<tr>
<td>Pregnancy</td>
<td>Cancer survivor</td>
</tr>
<tr>
<td>Renal</td>
<td>Heart transplantation</td>
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<tr>
<td>Chronic renal failure</td>
<td>Idiopathic hypercalcemia</td>
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<tr>
<td>Hemolytic-uremic syndrome</td>
<td>Kawasaki disease</td>
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<tr>
<td>Nephrotic syndrome</td>
<td>Klinefelter syndrome</td>
</tr>
<tr>
<td>Hepatic</td>
<td>Progeria (Hutchinson-Gilford syndrome)</td>
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<tr>
<td>Benign recurrent</td>
<td>Rheumatoid arthritis</td>
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<tr>
<td>intrahepatic cholestasis</td>
<td>Systemic lupus</td>
</tr>
<tr>
<td>Congenital biliary atresia</td>
<td>Erythematosis</td>
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<tr>
<td>Alagille syndrome</td>
<td>Werner syndrome</td>
</tr>
</tbody>
</table>

Metabolic disorders of dyslipidemia in youth

Disorders affecting LDL-receptor activity

There are five disorders expressed in pediatrics that result from mutations in the LDL-receptor (LDL-R) per se, or from mutations in other genes that impact LDL-R activity (Fig. 1). Elevated LDL-C levels can vary considerably in these five conditions, but each disorder manifests early atherosclerosis and premature CVD, prompting them to be called “the deadly quintet.”72,73 These disorders include FH,72,73 familial defective ApoB-100 (FDB),74 autosomal recessive hypercholesterolemia (ARH),75,76 sitosterolemia,77–80 and mutations in proprotein convertase subtilisin-like kexin type 9 (PCSK9).81,82 Each disorder warrants diet and drug therapy in childhood in an attempt to decrease atherosclerosis and subsequent CVD.

FH

FH heterozygotes. FH is the prototype for diagnosis and treatment of dyslipidemia in children. Children with heterozygous FH, an autosomal dominant disorder, present at birth67 and early in life69 with a two- to threefold elevation in levels of TC and LDL-C74,83,84 (Table 5). When children of an FH parent and a normal parent are screened, on average, half will be affected with FH and half will be normal; in these families, the cut point for LDL-C that minimizes misclassification is 160 mg/dL.69 FH affects 1 in 500, and is due to one of >900 different mutations in the LDL-
Rgene. FH heterozygous children and adolescents manifest increased carotid IMT, decreased brachial endothelial reactivity, but rarely overt CAD. Less than 10% of adolescent FH heterozygotes develop tendon xanthomas. In FH children, the null allele genotype was associated with greater carotid IMT, higher LDL-C, and a tendency to attenuated LDL-C–lowering with a statin, compared with receptor defective mutations. HDL-C is somewhat reduced in FH children compared to normal children, presumably secondary to the decreased uptake of IDL by the LDL-R, leading to increased IDL and enhanced transfer of TG from IDL to HDL in exchange for cholesterol ester. In

![Figure 1](image-url)

**Figure 1** Schema depicting five inherited disorders of lipoprotein metabolism that present in childhood with marked elevations of low-density lipoproteins (LDL), leading to premature atherosclerosis. Apolipoprotein B (ApoB), the major apolipoprotein of very low–density lipoproteins (VLDL) and LDL, is necessary for secretion of VLDL and uptake of its catabolic product, LDL, by the LDL receptor (LDL-R). Defects in the structure of ApoB (defective ApoB-100) or in the LDL-R (familial hypercholesterolemia [FH]) affect the normal binding, internalization, or recycling of the LDL-R. Autosomal recessive hypercholesterolemia (ARH) results from a defect in the ARH protein that normally interacts with the cytoplasmic component of the LDL-R, allowing tyrosine phosphorylation and internalization of the LDL-R. The proprotein convertase subtilisin-like kexin type 9 (PCSK9) is a serine protease that promotes degradation of the LDL-R. Gain-of-function mutations that increase PCSK9 activity decrease LDL-R activity. Proposed mechanisms include targeting of the LDL-R in the Golgi for degradation in the lysosome, interfering with the recycling of the LDL-R after secreted PCSK9 binds to the LDL-R at the cell surface, or directing the LDL-R to the lysosome to be degraded. The molecular defects responsible for sitosterolemia are caused by mutations in two genes that encode the half-transporters, ABCG5 and ABCG8, preventing their normal dual functions of limiting the absorption of cholesterol and plant sterols, and promoting their excretion from liver into bile. Adapted from Goldstein and Brown, with permission.

### Table 5: Levels of lipids, lipoproteins and apolipoprotein B in children with the most common lipoprotein abnormalities

<table>
<thead>
<tr>
<th>Lipoprotein disorder</th>
<th>Age</th>
<th>Plasma concentrations (mg/dL)</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Total-C</td>
</tr>
<tr>
<td>FH (n = 20)</td>
<td>8.0 ± 4.7</td>
<td>323 ± 44</td>
</tr>
<tr>
<td>FCHL (n = 65)</td>
<td>9.3 ± 4.7</td>
<td>220 ± 51</td>
</tr>
<tr>
<td>Hyper-ApoB (n = 11)</td>
<td>7.8 ± 4.6</td>
<td>200 ± 20</td>
</tr>
<tr>
<td>Normals (n = 110)</td>
<td>8.7 ± 1.8</td>
<td>162 ± 31</td>
</tr>
</tbody>
</table>

Apo, apolipoprotein; FH, familial hypercholesterolemia; FCHL, familial combined hyperlipidemia; HDL-C, high-density lipoprotein cholesterol; Hyper-ApoB, hyperapobetalipoproteinemia; LDL-C, low-density lipoprotein cholesterol.

*Data from Cortner and colleagues.
FH adults, about 50% of untreated male heterozygotes and 25% of untreated female heterozygotes will develop CAD by 50 years of age.

Treatment of FH heterozygotes includes a diet low in cholesterol and saturated fat that can be usefully supplemented with plant stanol esters, or plant sterol esters, and water-soluble fiber. Bile acid sequestrants are safe and moderately effective in FH heterozygotes, but compliance is an issue over the long term. The dose of the sequestrant required to achieve an LDL-C <160 mg/dL is related to baseline LDL-C level, and not to body weight; an adult dose is usually required. FH heterozygous children respond well to statins, which are well-tolerated. However, the addition of bile acid binding sequestrants or a cholesterol absorption inhibitor (CAI) to a statin (see also Pharmacologic therapy) is often necessary to achieve LDL-C goals. Niacin is generally not used to treat FH heterozygous children, unless LDL-C is persistently elevated and/or unusual hyper-TG, low HDL-C, or elevated Lp(a) are present.

FH homozygotes. About one in a million children inherit a mutant allele for FH from both parents, leading to LDL-C levels four- to eightfold above normal, often leading to precocious atherosclerosis and death from CAD in the second decade. FH homozygotes usually develop CAD in the second decade and atherosclerosis often affects the aortic valve, leading to life-threatening supravalvular aortic stenosis. Virtually all FH homozygotes have planar xanthomas by the age of 5 years, notably in the webbing of fingers and toes and across the buttocks. The seminal studies of such FH homozygous children by Goldstein and colleagues led to the discovery of the LDL-R, which was absent or markedly deficient in such children.

FH homozygotes respond somewhat to high doses of potent statins and to niacin. Because FH homozygotes have markedly diminished, if any, LDL-R activity, the statins and niacin both work by decreasing hepatic VLDL production, leading to decreased production of LDL. CAI also lowers LDL in FH homozygotes, especially in combination with a more potent statin. In the end, however, FH homozygotes will invariably require LDL apheresis every 2 weeks to effect further lowering of LDL into a range that is less atherogenic.

FDB. FDB results from mutations in the gene encoding ApoB-100, resulting in an impaired ability of the ApoB-100 ligand on LDL to bind to the LDL-R. The substitution of glutamine for an arginine at residue 3500 produces a defective ApoB-100 molecule whose binding of LDL to the LDL-R is deficient. Such deficient binding results in decreased clearance of LDL from plasma, leading to elevated LDL levels of mild, moderate, or marked degree. Heterozygotes for FDB are relatively common (eg, 1 per 1000 in Europeans). About 1 in 20 adult patients with FDB have tendon xanthomas, and appears clinically similar to adult heterozygous FH patients. Some adult patients with FDB develop premature CAD, but FDB itself is not a common cause of premature CAD. Treatment of FDB is similar to that for heterozygous FH.

ARH. Children with ARH are clinically similar to those with homozygous FH, although their LDL-C levels are not usually as elevated (between 350 and 550 mg/dL). In contrast to homozygous FH, both parents of an ARH child usually have normal lipoprotein profiles. An assay of LDL-R function in cultured skin fibroblasts from children with ARH is usually normal or mildly decreased. The ARH locus has been mapped to chromosome 1. At least six mutations have been found in the ARH gene in Sardinian and Lebanese kindreds. The ARH protein normally interacts with the cytoplasmic component of the LDL-R, and other cell surface–oriented molecules, allowing their tyrosine phosphorylation. The deficiency of the ARH protein prevents normal internalization of the LDL-R, leading to marked elevations of plasma LDL levels (Fig. 1). Those patients with ARH manifest a dramatic response to statins alone, or when combined with the CAI ezetimibe.

Sitosterolemia. Sitosterolemia (also called phytosterolemia) is a rare autosomal recessive disorder expressed in childhood and characterized by markedly elevated (>30-fold) plasma levels of plant sterols. This is due to hyperabsorption and inefficient excretion of plant sterols. TC and LDL-C levels can be normal, moderately elevated, or markedly elevated, depending on the dietary content of cholesterol and plant sterol. Sitosterolemics absorb a higher percentage of dietary cholesterol than normals, and they secrete less cholesterol into the bile, which decreases LDL-R activity and, in turn, increases LDL-C levels (Fig. 1).

The diagnosis of sitosterolemia should be considered, and plant sterols measured, in any child or adolescent who has xanthomas and yet a disproportionately low LDL-C level. As well, previously undiagnosed adults can mimic FH heterozygotes. Patients with sitosterolemia may develop aortic stenosis, as do those with homozygous FH. CVD can present in the first or second decade of life, but is usually delayed until early to middle adulthood.

The molecular defects responsible for sitosterolemia are caused by mutations in two genes that encode the half-transporters, ABCG5 and ABCG8. These two genes are on chromosome 2p, where they are located in a head-to-head orientation. ABCG5 and ABCG8 are expressed exclusively in human liver and intestine, the sites of the two metabolic abnormalities in sitosterolemia (Fig. 1). ABCG5 and ABCG8 have two normal functions: first, to limit the absorption of cholesterol and plant sterols; and, second, to promote their excretion from the liver into the bile.

Treatment of sitosterolemia begins with a diet markedly reduced in both cholesterol and plant sterols. Saturated fats are also restricted. Statins are less effective in this disorder because the high sterol content in the liver reduces cholesterol production. Bile aid sequestrants are quite effec-
tive as is ezetimibe. In one case report, a young sitosterolemia female treated with a combination of low-dose cholestanol and ezetimibe led to a marked improvement in plasma sterol concentrations, complete regression of xanthomatosis, resolution of carotid bruits, and improvement in her cardiac murmur.

**Mutations in PCSK9.** PCSK9 is a serine protease that degrades the LDL-R.\(^{81}\) Gain-of-function mutations that increase PCSK9 activity decrease LDL-R activity, producing a phenotype of hypercholesterolemia and premature CVD that is similar to FH.\(^{81,82}\) Loss-of-function mutations that decrease PCSK9 activity increase LDL-R activity, leading to a lifetime of low levels of LDL-C and a markedly reduced incidence of CVD.\(^{81}\) The site of action of PCSK9 on the LDL-R is not completely understood. One potential site of action is in the Golgi apparatus, where PCSK9 might target the LDL-R for degradation in the lysosome.\(^{81}\) Another possible pathway is that secreted PCSK9 binds to the LDL-R at the cell surface, leading to the internalization of a LDL-R/PCSK9 complex in conjunction with ARH\(^{81}\) (Fig. 1). PCSK9 may interfere with the recycling of the LDL-R from the endosome back to the cell surface, or direct the LDL-R to the lysosome to be degraded. It is not presently clear whether PCSK9 cleaves the LDL-R directly, or whether catalytic activity is necessary for either of these pathways.\(^{81}\) Patients with hypercholesterolemia and the gain-of-function PCSK9 mutation respond well to treatment similar to that used for FH heterozygotes.

### Disorders of overproduction of VLDL and LDL

Various phenotypes due to VLDL overproduction have been described, including FCHL, hyper-ApoB, LDL subclass pattern B, familial dyslipidemic hypertension, and syndrome X of Reaven.\(^{92,94}\) These phenotypes are pleiotropic, but the common denominator is the presence of increased small, dense LDL. Other aspects of the phenotypes are variably present and include hypercholesterolemia, hypertriglyceridemia, elevated ApoB with normal or borderline LDL-C, low HDL-C, insulin resistance, type 2 diabetes, glucose intolerance, hypertension, and CVD.\(^{92}\) Expression of these phenotypes is accentuated by the presence of obesity, particularly visceral adiposity. The metabolic syndrome seems inextricably intertwined with these phenotypes. No single gene defect has been described and the phenotypes are most likely due to the influence of oligogenic factors.\(^{92}\) Treatment of dyslipidemia (and other aspects) of these phenotypes can be successful starting in childhood.

**FCHL**

Goldstein and coworkers\(^ {93}\) described FCHL in families of survivors of myocardial infarction as an autosomal dominant disorder with variable lipid phenotypic expression: elevated LDL-C level alone (type IIA), elevated LDL-C with hyper-TG (type IIb), or normal LDL-C with hyper-TG (type IV). Although full-blown expression of FCHL can be delayed until adulthood,\(^ {83}\) it is not unusual to see children affected with FCHL express different lipoprotein profiles in families with premature CAD.\(^ {83}\) The average TC and LDL-C in children with FCHL is about 100 mg/dL lower than in those with FH, and the mean TG is elevated (Table 5). The ratio of LDL-C/ApoB is low in FCHL, indicating the presence of small, dense LDL particles, in contrast to FH where the LDL-C/ApoB ratio is high, manifesting the underlying large LDL particles (Table 5). In a pediatric lipid clinic population, FCHL was three times as prevalent as FH.\(^ {83}\) Also, total ApoB can be elevated in adolescents and young adults with FCHL before the combined dyslipidemia expresses itself.\(^ {70}\) Tendon xanthomas are not present in children or adults with FCHL. Individuals with FCHL often develop glucose intolerance, insulin resistance, hypertension, and visceral obesity.

Diagnosis of FCHL is made by finding a first-degree family member (often a parent or sibling) who has a different lipoprotein phenotype than the proband. The dyslipidemia of FCHL is often associated with an elevated number of small, dense LDL particles, which can be evaluated beyond the standard lipid profile by measuring ApoB or the level and size of lipoprotein subclasses by NMR, including small, dense LDL.\(^ {60}\) NMR has been studied in a few pediatric populations (see The metabolic syndrome).

### Metabolic basis of FCHL and other small, dense LDL syndromes

Abnormal free fatty acid (FFA) metabolism in FCHL and other small, dense LDL syndromes may reflect the primary defect in these patients (Fig. 2).\(^ {92,94}\) Impaired insulin-mediated suppression of hormone-sensitive lipase in adipocytes leads to an elevation in FFA.\(^ {92,94}\) Elevated FFA may drive hepatic overproduction of TG and ApoB, leading to a two- to threefold increased production of VLDL and the dyslipidemic triad (Fig. 2).\(^ {92,94,95}\) Insulin resistance also interferes with normal upregulation of lipoprotein lipase by insulin, leading to decreased lipolysis of TG in VLDL, as well as in intestinally derived TG-rich lipoproteins. This paradigm may also result from a defect in the normal effect of acylation stimulatory protein (Fig. 2), which is to stimulate the normal incorporation of FFA into TG in the adipocyte.\(^ {96}\)

Insulin resistance may also occur in the liver. Normally, insulin decreases hepatic gluconeogenesis by stimulating the phosphorylation of Fox01, preventing this transcription factor from entering the nucleus and activating gluconeogenesis.\(^ {97}\) In insulin resistance, Fox01 is not inhibited by phosphorylation, promoting gluconeogenesis, potentially contributing to abnormal hyperglycemia in the postprandial state. Finally, insulin normally increases hepatic TG production through upregulation of sterol regulatory element binding protein (SREBP)-1c.\(^ {97}\) Brown and Goldstein have
postulated that if there is selective insulin resistance affecting Fox01 but not SREBP-1c, this may contribute to hyper-TG as well as hyperglycemia.97

Finally, FFA and glucose compete as oxidative fuel sources in muscle, such that increased concentrations of FFA inhibit glucose uptake and result in insulin resistance.

**Genetic and molecular defects**

This group of disorders is clearly genetically heterogeneous, and a number of genes (oligogenic effect) can influence expression of increased small, dense LDL98 and low HDL-C99 in FCHL,100,101 and the other small, dense LDL syndromes.92,100,101 Recently, an orphan G protein–coupled receptor, called C5L2, was found to bind the acylation stimulatory protein with high affinity and promoted TG synthesis and glucose uptake,102 but it is not known if C5L2 is defective in hyper-ApoB patients.

Pajukanta and coworkers mapped the first major gene locus of FCHL to chromosome 1q21–23, and recently provided strong evidence that the gene underlying the linkage is the upstream transcription factor-1 (USF-1) gene.103 USF-1 regulates many important genes in lipid metabolism, including hepatic lipase, the activity of which is often increased in patients with these syndromes. Linkage of type 2 diabetes mellitus and FCHL to the USF-1 gene104 indicates that USF-1 may also contribute to the metabolic syndrome and type 2 diabetes.

**The metabolic syndrome**

The metabolic syndrome is of particular interest, given its recent epidemic in children, characterized by obesity, dyslipidemia, insulin resistance, glucose intolerance, and hypertension.42–48 In the past 20 years, the prevalence of adolescents with a BMI >95th percentile has increased by >50%.42 Prevalence of the metabolic syndrome in adolescents increases with severity of obesity and insulin resistance.45 Obese adolescents with the metabolic syndrome often have the dyslipidemic triad.42,45 Higher blood pressure levels in such adolescents increases carotid IMT, a marker for occult atherosclerosis.44 Of note, the metabolic syndrome in childhood predicts adult metabolic syndrome as well as CVD two to three decades later.105,106 The finding of acanthosis nigricans reflects the insulin resistance that is often present. In addition, biomarkers for increased risk of atherosclerotic disease, such as high-sensitivity C-reactive protein and adiponectin were increased in these obese children.45

NMR measurement of lipoprotein subclasses has provided some insights into their relationship to obesity and other aspects of the metabolic syndrome. Even in the gen-
eral population of children, TG, insulin, and relative weight in children were associated with size of VLDL (positive) and LDL (negative) particles. For white children, large VLDL, but not small VLDL, was notably higher than in black children across quintiles of waist circumference. In obese adolescents, the presence of fatty liver was associated with a pronounced dyslipidemic profile, characterized by large VLDL, small, dense LDL, and decreased large HDL concentrations. This proatherogenic phenotype was strongly related to the intrahepatic lipid content.

Clearly, overweight and obesity during childhood, as determined by BMI cut-off points, are strong predictors of obesity and CAD risk factors in young adulthood. In young adults, increasing numbers of adverse CV risk factors are associated with decreased brachial artery distensibility, more positive parental histories of CAD and hypertension, and greater carotid IMT.

Treatment of disorders of VLDL overproduction

Treatment starts with a low-fat diet to reduce the burden of postprandial chylomicrons and the atherogenic chylomicron remnants. Reduction to ideal body weight may improve insulin sensitivity and decrease VLDL overproduction. Regular aerobic exercise also appears important. Two classes of drugs, fibric acids and niacin acid, lower TG and increase HDL in adults and may also convert small, dense LDL to larger LDL. However, fibrates and niacin are not ordinarily used in pediatric patients. Statins are most effective in lowering LDL-C and the total number of atherogenic, small, dense LDL particles. In adolescents with FCHL or with the metabolic syndrome, drug treatment using a single agent, most often a statin, is reserved for those with a more marked elevation of LDL-C >160 mg/dL. Cholestyramine has also been used to treat pediatric patients with FCHL who have elevated LDL-C levels.

Use of metformin in the metabolic syndrome

Metformin has been used to treat obese hyperinsulinemic adolescents with the metabolic syndrome. Metformin can enhance insulin sensitivity, and reduce fasting blood glucose, insulin levels, plasma lipids, FFA, and leptin. In one report, 27% of the adolescents had acanthosis nigricans; none were judged to have the polycystic ovarian syndrome (PCOS).

PCOS

PCOS often presents in adolescence with menstrual disorders, acne, and hirsutism. Insulin resistance, considered one the underlying causes of PCOS, has increased substantially in the past decade, putting more adolescent girls at risk for PCOS and its complications, including elevated LDL-C or ApoB. After diet and weight control, the majority of endocrinologists use an estrogen/progesterone combination for treatment of PCOS. Only about one in three specialists consider metformin appropriate treatment in adolescents with PCOS; however, in obese teenagers with PCOS, almost 70% would use metformin. Adults with PCOS appear at high risk of CVD. Because increased carotid IMT has been observed in young adults with PCOS, earlier diagnosis and treatment of PCOS in adolescence may prevent its full-blown expression and CVD complications in adulthood.

Disorders of marked hyper-TG

Most hyper-TG in children and adolescents will be due to VLDL overproduction, resulting in one of the small, dense syndromes. There are a few rare disorders that are expressed as marked hyper-TG. These disorders include lipoprotein lipase (LPL) deficiency; defects in ApoC-II), the co-factor for LPL; and hepatic lipase (HL) deficiency. Once hyper-TG exceeds 1000 mg/dL, pancreatitis is a major concern, and eruptive xanthomas and lipemia retinalis can also be found. LPL deficiency presents at birth or in the first year of life, whereas expression of the other two disorders are usually delayed until adulthood. HL deficiency is associated with premature CAD, while LPL and ApoC-II defects are not.

Treatment of each of these disorders includes a very low fat diet (10% to 15% of calories) that can also be usefully supplemented with medium chain TG. Portagen, a soybean-based formula enriched in medium-chain TG, is available for infants with LPL deficiency. Lipid-lowering drugs are ineffective in LPL and ApoC-II disorders. HL deficiency responds to treatment with statins and, to a lesser extent, to fibrates.

Dysbetalipoproteinemia (type III hyperlipoproteinemia)

This unusual disorder usually presents with about equally elevated TC and TG levels, >300 mg/dL. The more common recessive form has a delayed penetration until adulthood and is due to the combination of an E2/E2 genotype (promotes slower uptake of TG-rich lipoproteins by the LDL-R) and overproduction of VLDL (Fig. 3). The rarer dominant form of the disorder is expressed as dyslipidemia starting in adolescence. A low-fat diet and treatment with fibrates, niacin, or statins are very effective.

Inherited disorders of HDL metabolism

Most of the time, low levels of HDL-C, associated with increased CVD, are secondary to VLDL overproduction, and are expressed as a component of the dyslipidemic triad. There are, however, primary HDL disorders that present as low HDL-C levels and CVD and that include familial hypoalphalipoproteinemia; ApoA-I mutations, and rarer disorders, such as Tangier disease, and lecithin cholesterol acyl transferase deficiency. One disorder, cholesteryl ester transfer protein
deficiency, often presents as high HDL-C, and may be associated with reduced risk of CVD. A low-fat diet is also indicated in children with inherited disorders of HDL metabolism. Drugs including niacin are rarely used in such children. In adults with the acute coronary syndrome, the infusion of recombinant ApoA-I Milano/phospholipid complexes for only 5 weeks significantly decreased percent atheroma volume as judged by intravascular ultrasonography. This experimental treatment has not been assessed in children with precocious atherosclerosis. In one study in adults with hypoalphalipoproteinemia, HDL-C levels increased from 16% to 91% with increasing doses of torcetrapib, a cholesteryl ester transfer protein inhibitor, that prevented the transfer of cholesterol ester from HDL for TG on the ApoB-containing lipoproteins (Fig. 2). However, when torcetrapib was given with atorvastatin to patients

![Figure 3](https://example.com/figure3.png)

**Figure 3** Sites of action of the six major lipid-altering drugs on exogenous and endogenous pathways of lipoprotein metabolism. (1) Inhibition of hydroxymethylglutaryl (HMG)-CoA reductase by statins; (2) binding of bile acids (BA) by sequestrants, interfering with their reabsorption by the ileal bile acid transporter (IBAT); (3) binding of a cholesterol absorption inhibitor to the Niemann Pick C1 Like 1 (NPC1L1), decreasing absorption of dietary and biliary cholesterol; (4) decreased mobilization of free fatty acids (FFA) by nicotinic acid, leading to decreased uptake of FFA by liver and reduced very low–density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), and low-density lipoprotein (LDL) production; (5) inhibition of triglyceride (TG) synthesis by omega-3 fatty acids; (6) upregulation of lipoprotein lipase (LPL) and decreased production of apolipoprotein (Apo) C-III, an inhibitor of LPL, by a fibric acid derivative, leading to decreased VLDL-TG. The hepatic cholesterol pool is decreased by the agents at steps 1, 2, and 3, each leading to an upregulation of the LDL receptor (LDL-R). ABCA1, ATP binding cassette protein; BA, XXX; CE, cholesteryl ester; CETP, cholesteryl ester transfer protein; CM, chylomicrons; CMR, chylomicron remnant; FC, free cholesterol; HDL, high-density lipoprotein; HL, hepatic lipase; LCAT, lecithin cholesterol acyltransferase; LRP, LDL receptor-like protein; MTP, microsomal triglyceride transport protein; SR-A, scavenger receptor type A; SRB1, scavenger receptor class B type 1.
with CVD, there was an excess total and CVD mortality, compared with those who received atorvastatin plus placebo. No data with torcetrapib are available in children.

**Elevated Lp(a)**

Lp(a) consists of one molecule of LDL, the ApoB-100 of which is covalently linked to one molecule of Apo(a) by a disulfide bond. Apo(a) is highly homologous to plasminogen, and when the Lp(a) level is elevated (>70 nmol/L for total Lp(a), >10 mg/dL for Lp(a) cholesterol), Apo(a) interferes with the thrombolytic action of plasmin, promoting thrombosis. Lp(a) also promotes atherosclerosis, particularly in some families with CAD. In adults, niacin and fibrates do not. In children with both an elevated estrogen can effectively lower Lp(a) levels, whereas the statins and fibrates do not. In children with both an elevated LDL-C >160 mg/dL, and Lp(a) level, one might consider a more aggressive use of a statin to lower the LDL-C level well into the normal range (<110 mg/dL). When LDL-C is determined using the Friedewald equation, Lp(a) cholesterol contributes to the LDL-C estimate. For more details concerning Lp(a), one is referred to a National Institutes of Health conference.

**Treatment of dyslipidemia in children and adolescents**

**Dietary therapy**

If the first lipoprotein profile is abnormal, then another profile is obtained at least 3 weeks later to confirm the first profile. If the average LDL-C is acceptable (<110 mg/dL), then education is provided, regarding eating and risk factors, with follow-up in 5 years. If the value is borderline (110–129 mg/dL), advice is given about risk factors, the Step I diet initiated, with re-evaluation in 1 year. If the LDL is elevated (≥130 mg/dL), common secondary causes are ruled out (thyroid, liver, and kidney disorders), parents and siblings screened, and a Step I diet started. If the LDL is not lowered to <130 mg/dL, then a Step II diet is initiated. Both diets require extensive dietary counseling and physician monitoring. The Step I diet calls for <10% of total calories from saturated fatty acids, no more than 30% of calories from total fat, <300 mg/day of cholesterol, and adequate calories to support growth and development at a desirable body weight. The Step I diet is evaluated for at least 3 months before prescribing the Step II diet. The Step II diet entails further reduction of the saturated fatty acid intake to <7% of calories, and reduced cholesterol intake to <200 mg/day.

**Safety and efficacy of dietary therapy in children and adolescents**

The efficacy and safety of diets low in total fat, saturated fat and cholesterol to lower LDL-C levels in youth have been demonstrated across the age spectrum of pediatric patients, eg, from the age of 7 months to the age of 7 years and from 7 to 11 years in STRIP17–19 and from the ages of 8 to 10 years throughout adolescence in DISC.20–22 In some studies, there were lower intakes of calcium, zinc, vitamin E, and phosphorus, on low-fat diets. Therefore, although normal growth is achieved and maintained on low-fat diets, attention needs to be paid to ensure adequate intake of these key nutritional elements.

The use of margarines (about three servings daily) high in either plant stanol esters23,24 or plant sterol esters25 can reduce LDL-C an additional 10% to 15% when added to a low-fat diet. Water-soluble fibers,26 such as psyllium,27,28 can also provide an additional 5% to 10% lowering of LDL-C.

Use of a soy protein beverage does not appear to lower LDL-C, but does lower VLDL-C and TG and increases HDL.128,129 Compared with placebo, supplementation of a low-fat diet with an omega-3 fatty acid (docosahexaenoic acid 1.2 g/day) did not lower LDL-C, but changed the distribution between LDL subclasses with a significant 91% increase in the largest LDL and a 48% decrease in the smallest LDL subclass.130 Garlic extract therapy does not lower LDL-C in hyperlipidemic children.131

Overall, a diet low in fat in children with dyslipidemias appears to be both safe and efficacious when performed under health supervision. Medical support is necessary to continue to reinforce good dietary behaviors and to ensure nutritional adequacy.

**Effect of a low-fat diet in childhood on future CVD in adulthood**

That a low saturated fat, low-cholesterol diet in childhood will prevent CVD in adulthood can only be inferred from epidemiologic studies, where children from countries with a lower prevalence of CVD had lower TC levels than those children from countries with higher CVD and TC levels.12,13 Insulin resistance is promoted already in childhood by obesity. In that regard, in STRIP, low saturated–fat dietary counseling starting in infancy improved insulin sensitivity in 9-year-old healthy children.132 Further, in STRIP, a low saturated–fat diet introduced in infancy and maintained during the first decade of life was associated with enhanced endothelial function in boys, but not in girls, and was mediated in part by the diet-induced reduction in TC.133 In the same Finnish study, at 10 years, 10% of the intervention girls were overweight compared with 19% of the control girls, but this significant difference was not seen in the boys.134

**Pharmacologic therapy**

There are six main classes of lipid-altering drugs (Fig. 3). These include: (1) inhibitors of HMG-CoA reductase (the statins); (2) bile acid sequestrants; (3) CAIs; (4) niacin
Bile acid sequestrants

Bile acid sequestrants were the only class of drugs recommended by NCEP for pharmacologic lipid-lowering therapy because of their long track record of safety for three decades. The sequestrants have never been approved by the FDA for use in children. These agents have significant tolerability issues as well as providing only a modest LDL-C reduction. A 16.9% decrease in LDL-C was found that 52 of 63 children discontinued cholestyramine treatment after an average of 21.9 months, secondary to gritty taste and gastrointestinal complaints. The second-generation sequestrant, colesevelam, has a greater affinity for bile salts, and can therefore be used in a lower total dose, which is provided as a tablet (total dose six tablets per day). In comparison with first-generation sequestrants, colesevelam is associated with less-annoying side effects, such as constipation and gritty taste, and does not interfere with absorption of other drugs.

In randomized clinical trials, cholestyramine did not affect height velocity. Fat-soluble vitamins were maintained, except the BAS group had significantly lower 25-hydroxyvitamin D than the placebo group. One girl had low folate and high homocysteine levels.

HMG-CoA reductase inhibitors

Statins are widely used to lower TC and LDL-C in adults. Numerous randomized controlled trials demonstrated the safety and efficacy of the statins in male and female adolescents with FH. A meta-analysis of six of these trials showed high efficacy for LDL-C and ApoB-lowering and no increase in side effects, compared with placebo groups. Atorvastatin, lovastatin, pravastatin, and simvastatin are approved by the FDA for use in adolescents with FH.

Using carotid IMT as a surrogate marker for atherosclerosis, Wiegman and colleagues demonstrated that a mean 24% reduction in LDL-C in FH heterozygote children and adolescents with pravastatin produced a significant decrease in carotid IMT, compared to those on placebo. A follow-up study of this Dutch cohort showed that younger age at statin initiation was an independent predictor of effect of treatment on carotid IMT. Early statin therapy also restores endothelial function in children with FH. Early intervention with statins appears likely to be effective at reducing future atherosclerosis and CVD in those with FH.

Statins may also be useful in those adolescents with FCHL and the metabolic syndrome who have an LDL-C >160 mg/dL after diet and weight control, multiple risk factors, or a family history of premature CVD. Even in young women with PCOS, there is increased carotid IMT, again suggesting that greater attention be paid to managing dyslipidemia and other CVD risk factors early in life.

Side effects of the statins in children and adolescents

Liver and muscle

Increases in liver function tests up to three times the upper limit of normal have been reported in several adolescents treated with higher doses of simvastatin (40 mg/day) and atorvastatin (20 mg/day). In a meta-analysis, prevalence of an elevated alanine aminotransferase in the statin group was 0.66% (3 per 454). Instances of asymptomatic increases (>10-fold) in creatine kinase, while unusual, have
been reported in adolescents receiving statin therapy.27 No cases of rhabdomyolysis have been reported.29–37 Such adolescents are monitored for elevations in hepatic transaminases and creatine kinase concentrations.

Special issues in young females

Adult women with FH and clinical evidence of CAD may be more responsive to LDL-C–lowering therapy than similarly affected men, as assessed by regression of coronary plaques and tendon xanthomas.139 The overall favorable safety profile of statin therapy in adult women with CVD is well-documented; however, fewer studies have examined the effects of the statins in adolescent girls.32,35,36 Nevertheless, there has been no adverse effect on growth and development or on adrenal and gonadal hormones.32,35,36 One study31 found a small increase and another study a small decrease32 in dehydroepiandrosterone sulfate.

It is important to note that statins are contraindicated during pregnancy because of the potential risk to a developing fetus. Hence, these drugs should be administered to adolescent girls only when they are highly unlikely to conceive.

Because of these concerns, the long-term commitment to therapy, and the fact that CAD often occurs after menopause, some believe that statins should not be used to treat young females.

Although treatment of adolescent patients with FH is indicated, especially in those with a strong family history of premature CAD, additional studies are needed to document the long-term safety of statin therapy, and to determine its potential effects on prevention of atherosclerosis and coronary events.

Metabolic syndrome: Beyond dyslipidemia

If LDL-C is <160 mg/dL statin therapy is not recommended. In addition to the paramount importance of a low-fat diet, exercise, and weight reduction, metformin has been used in several studies of obese adolescents with the metabolic syndrome and hyperinsulinemia.106,107

Treatment of dyslipidemia secondary to other diseases

Type 1 diabetes

Children with type 1 diabetes often have a dyslipidemia, the severity of which is related to diabetic control. The American Diabetes Association recommends dietary and other hygienic measures as the first step in the treatment of these children. However, if the LDL-C is >160 mg/dL after such treatment, the American Diabetes Association panel strongly recommends pharmacologic treatment, including use of statins in adolescents.41 This recommendation is based, in part, on the high risk of CVD in adults with type 1 diabetes, and upon the consistent finding of abnormal carotid IMT in children with type 1 diabetes.

Nephrotic syndrome

Dyslipidemia in children with the nephrotic syndrome can be marked. For example, average LDL-C level is close to that found in heterozygotes with FH (Table 1). TG levels can approach 300 mg/dL. The combined elevation of LDL-C and VLDL-C can produce a hypercholesterolemia close to 400 mg/dL.140 Twenty percent of patients with nephrotic syndrome are unresponsive to steroid administration, most cases of which can be attributed to focal segmental glomerulosclerosis. Such individuals with an LDL-C >160 mg/dL may be at increased risk for developing atherosclerosis and CVD,140 and may warrant treatment with a statin.125

Conclusions

The importance of identifying children and adolescents at enhanced risk for atherosclerosis has been emphasized further by the recent epidemic of obesity and the metabolic syndrome in American youth. Dietary and hygienic measures are the first form of treatment. Certain adolescents with more marked dyslipidemia will require drug treatment. Treatment with both diet and drugs appears safe and efficacious in this age group, but longer term data are needed. An updated diagnostic and treatment algorithm is needed to reflect the changes required by recent advances in this field.

References


