Detection and Treatment of Children and Adolescents with Dyslipidemia

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Introduction

Dyslipidemia can present a particular challenge in infants, children, and adolescents due to their size, age, effects of sexual development, other medical conditions, use of medications, and demands of hygienic or pharmacologic treatment [1, 2]. In addition, there is controversy about screening for dyslipidemia in youth, and concerns about the long-term safety and efficacy of drug treatment starting in adolescence, and whether treatment starting early in life will decrease cardiovascular disease (CVD) events in adulthood [1, 2].

The clinical and scientific data supporting a strong link between pediatric dyslipidemia and other CVD risk factors and the early lesions of atherosclerosis in adolescence and young adulthood have expanded considerably over the past several decades [1, 2]. This chapter reviews these data, which provide a basis for updated recommendations and approaches to dyslipoproteinemia in youth [1, 2]. These data are conceptually divided into those related to youth with inherited disorders such as familial hypercholesterolemia (FH), and those from long-term observational studies of entire populations of children.

Disorders of Low-Density Lipoprotein Metabolism in Children and Adolescents Due to Altered LDL Receptor Activity

Familial Hypercholesterolemia

Heterozygous FH is the most common inherited disorder of lipoprotein metabolism with a prevalence of between 1/300 and 1/500. Due to founder effects, FH has a higher incidence in French-Canadians, Afrikaners, Christian Lebanese, and Finns. The University College London (UCL) low-density lipoprotein receptor (LDLR) variant database includes over 1288 different variants reported in FH patients, 79 % of whom are likely to be disease causing [7]. Examination of children aged 1–19 years, born to one parent with FH and a normal parent, showed that 45 % were affected with a mean low-density lipoprotein-cholesterol (LDL-C) of 230 mg/dL, compared to a mean LDL-C of 110 mg/dL in the unaffected children [8]. Cut points, which minimized misclassification, were 160 mg/dL for LDL-C and 235 mg/dL for total cholesterol (TC). FH should be considered in any child with an LDL-C or TC above these cut points. Finally, the percentage of FH children in the first decade

Unfortunately, Dr. Kwiterovich passed away on August 15, 2014 at the age of 74. He was an esteemed colleague and one of the world's foremost authorities on pediatric dyslipidemias. The scientific community will miss him dearly. The Editor really appreciates his seminal contribution to this book.

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(52%) significantly exceeded that in the second (39%) ($P<0.01$) [8]. We now know that the dearth of affected FH adolescents here were due to a 10–20% reduction that occurs in LDL-C in both FH and normal children during adolescence that can cause a false-negative result. The mechanism of lowering of LDL-C during adolescence is not elucidated [9].

Children are usually screened because a parent has hypercholesterolemia, or there is a family member with premature CVD. Such selective screening identifies an unacceptably low number of children with FH. In one study, a positive family history for coronary artery disease (CAD) was detected in 18.3% of 71 children with TC >95th percentile, and only 11.8% of 34 children with presumed heterozygous FH [10]. In contrast, universal lipid screening will detect 96% of FH children aged 1–9 years with a 1% false-positive rate [11]. Screening for FH should occur before adolescence to avoid the false negatives that can occur during this time of life.

FH heterozygotes usually are healthy children with no physical findings. About 5–10% manifest Achilles tendon xanthomas in the second decade. Increased carotid intima media thickness (cIMT) and decreased vascular reactivity start in FH children around 8–10 years of age [12, 13]. Children with FH are at a high risk of premature CVD as adults without treatment; 25% of males and 12% of females develop CVD by 40 years of age, and 50% of males and 25% of females do so at 50 years of age [14]. Coronary plaque burden was assessed by noninvasive computed tomography coronary angiography (CTCA) in 140 asymptomatic statin- treated middle-aged adult patients with FH. The extent of CAD was related to gender and TC levels and ranged from absence of plaque in one out of six patients to extensive CAD with plaque causing >50% lumen obstruction in almost a quarter of patients with FH [14].

FH Homozygotes If two parents are FH heterozygotes, there is a one in four chance that their child may inherit two faulty LDLR genes. These children may be true homozygous or compound heterozygous for two mutant alleles of *LDLR*. FH homozygotes are rare with a prevalence of about one in a million (1/500×1/500×1/4.) Thus, it is unlikely that most physicians will ever see an FH homozygote child. FH homozygotes usually have TC levels between 600 and 1000 mg/dL; planar xanthomas by the age of 5 years, notably in the webs of fingers and toes, the knees, and buttocks; and often develop life-threatening supravalvular aortic stenosis and CAD in the second decade [15]. FH homozygotes may require CTCA at baseline to exclude or investigate coronary atherosclerotic lesions. If a previous child has homozygous FH, prenatal diagnosis can be performed in future pregnancies to detect FH homozygotes.

Treatment of Youth with Heterozygous FH A diet low in total fat, saturated fat, *trans* fat, and cholesterol in youth with FH can be safely used to lower LDL-C about 5–10% [1–4]. The diet can be supplemented with plant sterols or stanols (usually purchased as commercially available margarines) to decrease cholesterol absorption and lower LDL-C another 5–10%. Most FH heterozygous children require high doses of more potent statins, or the addition of a bile acid sequestrant (BAS) or ezetimibe to a statin, to lower LDL-C sufficiently, i.e., to below the mean of normal children (<110 mg/dL) [1]. Decreased LDLR activity can also lead to moderate hypertriglyceridemia due to decreased uptake of intermediate-density lipoprotein (IDL; see above). High-density lipoprotein-cholesterol (HDL-C) levels can be normal, borderline, or low.

Treatment of FH Homozygotes FH homozygotes respond somewhat to high doses of statins (with a fall in LDL-C of between 100 and 200 mg/dL) [1]. Niacin can lower LDL-C in FH homozygotes about another 25%. Both statins and niacin decrease production of hepatic very low-density lipoprotein (VLDL), leading to decreased production of LDL (Fig. 5.1). Ezetimibe, a cholesterol absorption inhibitor (CAI), lowers LDL-C another 25% in FH homozygotes and has a Food and Drug Administration (FDA) approval [1]. Such triple-lipid-altering therapy in FH homozygotes may lower LDL-C to a range closer to that found in FH heterozygotes. FH homozygotes

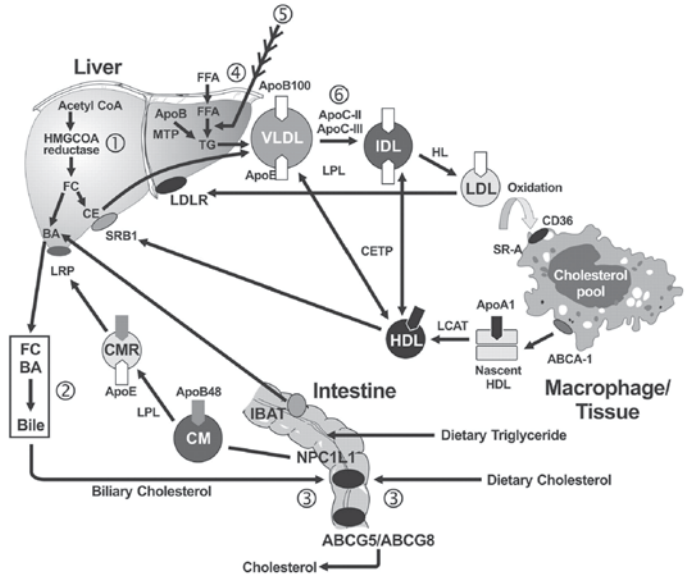

Fig. 5.1 Three major pathways of plasma lipoprotein metabolism are shown: (*1*) transport of dietary (exogenous) fat (*left*), (*2*) transport of hepatic (endogenous) fat (*center*), and (*3*) reverse cholesterol transport (*bottom*). Sites of action of the six major lipid-altering drugs on exogenous and endogenous pathways of lipoprotein metabolism are: (*1*) inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A (HMGCoA) reductase by statins; (*2*) binding of bile acids by sequestrants, interfering with their reabsorption by the ileal bile acid transporter (IBAT); (*3*) binding of a cholesterol absorption inhibitor to the Niemann–Pick C1L1, decreasing the absorption of dietary and biliary cholesterol; (*4*) decreased mobilization of free fatty acids (FFA) by niacin, 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 TG synthesis by ω-3 fatty acids; (*6*) upregulation of lipoprotein lipase (LPL) and decreased production of apoC-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 LDLR. *LCAT* lecithin–cholesterol acyl transferase, *ABCA-I* ATP-binding cassette protein A-I, *ABCG* ATP-binding cassette protein G, *BA* bile acids, *CE* cholesteryl esters, *CM* chylomicrons, *CMR* chylomicron remnants, *SR-A* class A scavenger receptor, *SRB1* class B scavenger receptor. (Reproduced with permission from P. O. Kwiterovich, Jr.)

often require weekly LDL apheresis to lower LDL-C to a less atherogenic range. There is evidence that drastic lowering of LDL-C by LDL apheresis increases longevity in FH homozygotes and decreases cardiovascular morbidity in FH heterozygotes refractory to or intolerant of statins [15]. If LDL apheresis cannot be performed, then hepatic transplantation may be considered. The results of liver transplant are inconsistent. In one report, a 5-year-old FH child homozygous for the p.W577R *LDLR* defect had significant progression of coronary atherosclerosis despite intensive treatment with diet, statins, colestipol, and LDL-apheresis; at 16 years of age, liver transplantation was performed leading to normalization of LDL-C, and regression of symptomatic coronary atherosclerosis and xanthomas 9 years later [16]. In another report, a 14-year-old girl presented with severe bilateral coronary ostial stenosis and tight supravalvular aortic narrowing 10 years *after* liver transplantation, despite normalization of the lipids and apparently died of sepsis [17].

Newer Pharmacologic Treatment of FH Homozygotes The safety and efficacy of mipomersen, an antisense inhibitor of apolipoprotein B (apoB), was studied in 51 FH homozygotes, aged 12 years or older, on maximum lipid-altering therapy, in a randomized, placebo-controlled 26-week study, in which 34 patients were assigned to mipomersen, 200 mg/week, and 17 to placebo [18]. Of 46 patients who completed the study, the

mean fall in LDL-C of 24.7% in the mipomersen group versus 3.3% in the placebo was observed. Side effects included injection site reactions in 76% of the patients in the mipomersen group versus 24% in the placebo group. Four patients in the mipomersen group had increases in liver function tests exceeding three times the upper limit of normal with none in the placebo group. The drug, which was developed by Isis Pharmaceuticals, was approved in 2012 in the USA as an orphan drug and is marketed under the brand name of Kynamro by *Genzyme*. Kynamro was approved with a *Risk* Evaluation and Mitigation Strategy (REMS) which requires certification of pharmacies and prescribers, as well as documentation that the drug is being properly used with each new prescription. Possible liver toxicity and fatty liver will be monitored along with a variety of general medical side effects.

Inhibitor of Microsomal Triglyceride Transfer Protein in FH Homozygotes In a dose escalation study, the safety, efficacy and tolerability of a microsomal triglyceride transfer protein (MTP) inhibitor, lomitapide, was studied for 26 weeks or longer in six FH homozygotes aged 18 years or older and off all lipid-altering therapy for 4 weeks [19]. At a maximum dose of 1 mg/kg, inhibition of MTP caused a 50% reduction in the synthesis of LDL leading to close to 50% reduction in LDL-C. At the maximum therapy, accumulation of hepatic fat ranged from less than 10% to more than 40%. Cuchel et al. [20] did a single-arm, open-label, phase 3 study of lomitapide for 26 weeks in 29 adult FH homozygotes on current lipid-altering therapy. The lomitapide dose was escalated on the basis of safety and tolerability from 5 mg to a maximum of 60 mg a day. The median dose of lomitapide was 40 mg/day, which produced a 50% decrease in LDL-C. Five patients had moderately elevated LFTs which fell to normal after the study was completed; hepatic fat increased to 10%. In December 2012, the FDA in the USA approved lomitapide marketed as Juxtapid by Aegerion Pharmaceuticals. Juxtapid is also available only through a restricted REMS program.

Monoclonal antibodies that inhibit proprotein convertase subtilisin/kexin type 9 (PCSK9) activity have been developed and lower LDL-C up to 50%, by blocking PCSK9 and its effect on decreasing LDLR. This new agent can be used either in combination with a statin or alone in those with statin intolerance (see below). However, no data are available on the use of these PCSK9 inhibitors in children with heterozygous FH or FH3 due to PCSK9 mutations.

Ex vivo gene therapy Novel long-term persisting vectors derived from adeno-associated viruses and lentiviruses, are now available and investigations are under way to determine their safety and efficacy in preparation for clinical application for a variety of diseases including homozygous FH [21].

Phenocopies of FH Homozygotes Other primary disorders affecting LDLR activity (see below) can also present with planar, tendon, or tuberous xanthomas similar to FH homozygous children, and so can adolescents with the dominant form of dysbetalipoproteinemia (see below). Patients with secondary disorders of dyslipidemia accompanied by xanthomas include biliary cirrhosis, congenital biliary atresia, Alagille syndrome, myelomas, and Wolman disease [3, 4]. These disorders have other clinically salient findings to distinguish them from FH homozygotes.

Familial Ligand-Defective apoB-100

Heterozygotes with familial ligand-defective apoB-100 (FDB) may present with normal, moderately elevated, or markedly increased LDL-C [14, 18]. Hypercholesterolemia is usually not as severe in FDB as in FH heterozygotes. About 1 in 20 of affected patients with FDB has tendon xanthomas and more extreme hypercholesterolemia. FDB represents a small fraction of patients with premature CAD, i.e. no more than 1%. In FDB patients, there is delayed removal of defective apoB-100 LDL from blood despite normal LDLR activity but the clearance of triglyceride (TG)-enriched particles, VLDL remnants and IDL, is not affected. The most commonly recognized mutation in FDB is a missense mutation (p.R3500Q)

in the LDLR-binding domain of apoB-100 [22]. The frequency of FDB heterozygotes is about 1 in 1000 in central Europe [5], but appears less common in other populations. Dietary and drug treatment of FDB is similar to that used for FH heterozygotes.

Heterozygous FH3

The clinical presentation of heterozygous FH3 is indistinguishable from FH heterozygotes [5, 6]. FH3 results from mutations in PCSK9 [5, 6]. PCSK9 facilitates the degradation of LDLR and more recent data expand the potential pathways that may be involved in the molecular effect of PCSK9 on degradation of LDLR [6]. Gain-of-function mutations that increase PCSK9 activity decrease LDLR activity, producing marked hypercholesterolemia. Conversely, loss-of-function mutations that decrease PCSK9 activity increase LDLR and produce levels of LDL-C < 80 mg/dL and decreased CAD.

Autosomal Recessive Hypercholesterolemia

Autosomal recessive hypercholesterolemia (ARH) is a rare autosomal recessive disorder that usually presents with LDL-C in between those in FH heterozygotes and FH homozygotes [5]. Their onset of CAD often occurs later than that in FH homozygotes. Children with ARH often have large tuberous xanthomas. ARH is more prevalent in Sardinian families. Parents are consanguineous and most often have normal LDL-C levels. LDLR activity in ARH fibroblasts is normal, but it is defective in lymphocytes where LDL are not internalized normally. Recessive null mutations in a novel gene called LDL receptor adaptor protein 1 (LDLRAP1; also known as ARH) cosegregate with hypercholesterolemia in families with ARH [5]. LDLRAP1 protein contains a conserved phosphotyrosine-binding domain, and functions as an accessory adaptor protein that interacts with the LDLR via its cytoplasmic domain, enabling LDLR to engage with the clathrin-coated pit machinery for endocytosis. Fortunately, youth with ARH respond quite dramatically to treatment with statins and ezetimibe. A BAS may also be added to the statin for further reduction in LDL-C. Despite this therapy, some ARH patients, especially those with CAD, may also require LDL apheresis. [23].

Sitosterolemia

Children and adolescents with this rare, autosomal recessive disorder can present with normal to markedly elevated TC and LDL-C levels, tendon and tuberous xanthomas, premature CAD, and aortic stenosis [5]. Homozygotes manifest abnormal intestinal hyperabsorption of plant sterols (sitosterol, campesterol, and stigmasterol), shellfish sterols, and cholesterol. In normal humans, very little plant sterols are absorbed and plasma plant sterol levels are low (0.3–1.7 mg/dL) constituting < 1% of plasma total sterols. The levels of total plant sterols (13 to 37 mg/dL) in patients with sitosterolemia are very elevated and represent 7–16% of the total plasma sterols. Sitosterolemia patients often present in childhood with striking tuberous and tendon xanthomas, despite normal or FH heterozygote-like LDL-C levels. The diagnosis is made by documenting elevated plant sterols using high-performance liquid chromatography. The parents and obligate heterozygous siblings usually have normal LDL-C and only slightly higher plant sterol levels. Two ATP-binding cassette (ABC) half-transporters, ABCG5 and ABCG8 [5], normally limit the intestinal absorption of plant sterols and cholesterol and promote their excretion (Fig. 5.1). Sitosterolemia is caused by two mutations in either of the two adjacent genes that encode ABCG5 or ABCG8, thereby enhancing absorption of dietary sterols and reducing hepatic excretion of sterol into bile (Fig. 5.1). This leads to an increased hepatic content of cholesterol and plant sterols, suppression of LDLR, inhibition of LDLR synthesis, and elevated LDL-C.

Dietary treatment is *paramount* in sitosterolemia. In addition to the standard low-cholesterol, low-saturated-fat diet, plant foods with a high plant sterol content, such as oils and margarines

[1, 2], must be avoided. BAS are particularly effective in lowering plant sterol levels. Ezetimibe is also quite effective and approved by FDA for use in patients with sitosterolemia [24]. These patients respond less well to statins because 3-hydroxy-3-methylglutaryl-coenzyme A (HMGCoA) reductase is already inhibited from the increased hepatic sterol content.

Cholesterol 7α-Hydroxylase Deficiency

Several patients have been described with a deficiency in the rate-limiting enzyme of bile acid synthesis, cholesterol 7α-hydroxylase, which converts cholesterol into 7α-hydroxycholesterol (Fig. 5.1, upper left). Thus, hepatic cholesterol can increase, decreasing LDLR and increasing levels of LDL-C and TG-enriched remnants, leading to both hypercholesterolemia and hypertriglyceridemia [25]. As with patients with sitosterolemia, these subjects are relatively resistant to statin therapy.

Lysosomal Acid Lipase Deficiency

Wolman Disease and Cholesteryl Ester Storage Disease

Human lysosomal acid lipase (LAL) is essential for the intralysosomal hydrolysis of LDL-derived cholesteryl ester (CE) into free cholesterol (FC). There are two general presentations of LAL deficiency, Wolman disease and CE storage disease (CESD), both autosomal recessive traits at the LAL locus. Wolman disease, associated with deficient LAL activity, leads to massive intralysosomal accumulation and is always fatal in early infancy. In contrast, CESD is characterized by very low levels of LAL activity that is sufficient to allow survival of the affected patients into adulthood. In one report, the splice defect in Wolman, which affects one of the invariable nucleotides of the splice consensus sequences (position +1), does not permit any correct splicing, whereas the defect observed in CESD (position −1) allows some correct splicing (3% of total LAL messenger RNA (mRNA)) and therefore the synthesis of some functional enzyme [26].

Metabolic Derangement There is an abnormal responsiveness of the LAL-deficient cells to the regulatory actions of LDL, namely decreased formation of FC from CE leading to decreased LDL-mediated suppression of the activity of HMGCoA reductase and to decreased LDL-mediated activation of cellular CE formation [27]. The enhanced synthesis of cholesterol contributes to increased VLDL production, increased apoB synthesis, leading to increased secretion of VLDL, elevated LDL, and low HDL (in CESD) [28].

Clinical Presentation Wolman disease is fatal with a very short life span, usually under 1 year [29]. Marked abdominal distension, persistent and forceful vomiting, watery stools, severe anemia, and failure to thrive start in the first weeks of life. Hepatosplenomegaly is invariably present and may be massive. The most striking feature is calcification of the adrenal glands. Circulating vacuolated lymphocytes and foam cells in bone marrow are almost constant findings.

In contrast to Wolman disease, CESD is characterized by a mild and relatively variable phenotype [29]. The principal and sometimes only sign, hepatomegaly, is evident at birth or in early childhood, increases with time, and eventually leads to hepatic fibrosis. Acute or chronic liver failure and jaundice have been observed and may require liver transplantation. Recurrent abdominal pain occurs frequently. Children and adults with CESD can present with a combined hyperlipidemia. Patients with CESD can survive for longer periods of time [29], and some adults with CESD develop premature atherosclerosis.

Treatment Infants with Wolman disease may respond either to transplantation of unrelated human leukocyte antigen (HLA)-mismatched umbilical cord-blood-derived stem cells, which restored normal LAL activity before permanent end-organ damage, [30], or to hematopoietic cell transplantation [31]. In a 9-year-old child with CESD, a notable combined dyslipidemia was shown to be due to increased formation of VLDL, increased biosynthesis of apoB and cholesterol, and low HDL-C [28]. Lovastatin (maximum dose 20 mg twice daily) reduced both the rate of cholesterol and apoB synthesis and the secretion of

Table 5.1 Levels of lipids, lipoproteins, and apoB in children with the most common genetic lipoprotein abnormalities. (Data are from Cortner et al. [51])

Lipoprotein disorder	Age (years)	Plasma concentrations (mg/dL)					
		TC	TG	HDL-C	LDL-C	APOB	LDL-C/APOB
Heterozygous, FH ($n=20$)	8.0±4.7	323±44	86±36	44±8	262±45	219±42	1.22±0.22
FCHL ($n=65$)	9.3±4.7	220±51	120±91	45±11	149±48	153±39	0.98±0.19
HyperapoB ($n=11$)	7.8±4.6	200±20	91±35	52±7	130±16	138±21	0.95±0.10
Normals ($n=110$)	8.7±1.8	162±31	70±39	51±10	97±27	85±20	1.15±0.20

TC total cholesterol, *TG* triglycerides, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *APOB* apolipoprotein ß, *FH* familial hypercholesterolemia, *FCHL*, familial combined hyperlipidemia

VLDL, leading to significant reductions in TC, LDL-C, and TG in CESD [28]. Clinical trials are ongoing to evaluate enzyme replacement therapy with recombinant human LAL enzyme.

Disorders of LDL Metabolism in Children and Adolescents Due to Overproduction of VLDL/IDL/LDL

Familial Combined Hyperlipidemia

Goldstein and colleagues [32] ascertained families in Seattle in whom the proband had premature myocardial infarction before 60 years of age. A family was considered to have familial combined hyperlipidemia (FCHL) if the proband had one of three lipid patterns, i.e., elevated TC (increased LDL alone), elevated TG (increased VLDL alone), or both TC and TG (increased LDL and VLDL) were elevated *and* a first-degree relative was affected with a *different* lipid pattern than the proband [32]. The FCHL families suggested this lipoprotein disorder was an autosomal dominant with delayed expression into adulthood.

Metabolic Abnormalities in FCHL The hypertriglyceridemia so common in FCHL is due to overproduction of hepatic TG-rich VLDL [33]. In plasma, there is increased activity of CETP, that facilitates the exchange of TG in VLDL for CE in LDL and HDL, leading to a CE-enriched VLDL and TG-enriched LDL and HDL. As the TG in LDL and HDL are hydrolyzed by hepatic lipase (HL), increased small dense LDL and cholesterol-depleted HDL are produced. Thus, elevated small LDL often accompanies the significant hypertriglyceridemia in FCHL. This phenotype is also referred to as hyperTG hyperapoB and is strongly associated with CVD, type 2 diabetes, visceral obesity, and the metabolic syndrome [34].

Insulin resistance is often an important etiologic component and results in increased delivery of free fatty acids (FFA) to the liver due to increased peripheral lipolysis of TG in adipocytes. Increased hepatic VLDL production occurs due to increased substrate availability of FFA, increased lipogenesis, and decreased apoB-100 degradation (leading to increased apoB synthesis).

Other abnormalities of TG metabolism in FCHL include the CE enrichment in the IDL remnants from VLDL, and postprandial hypertriglyceridemia.

Relevance of FCHL and hyperTG hyperapoB to Youth As the field of pediatric hyperlipidemia evolved, it became clear from observations from a number of pediatric lipid clinics, such as those reported by Cortner et al. [35] (Table 5.1), that FCHL was more prevalent than FH in their dyslipidemic families. hyperapoB was also expressed in this age group. As judged by the low LDL-C/apoB ratio, those youth with FCHL had increased numbers of small dense particles (Table 5.1). Those with FH had elevated LDL-C/apoB ratio indicating increased numbers of larger, more cholesterol-enriched particles. These results reflected the metabolic defects of increased production of VLDL/IDL/LDL in FCHL and decreased catabolism of IDL and LDL in FH. Finally, as judged by the extent of their apoB elevations, some youth judged to have FCHL had as many atherogenic LDL particles as those found in FH children. However, the LDL-C level was much lower in those with FCHL (Table 5.1).

The question of delayed expression of FCHL is not completely resolved. The simplest explanation is that differences are related to: mode of ascertainment, i.e., proband with premature myocardial infarction [33] or angiographically documented coronary atherosclerosis [36], versus referral of youth with known combined hyperlipidemia to lipid clinics [35, 37]; false negatives due to significant decrement of LDL during adolescence; and genetic heterogeneity especially given the apparent oligogenic nature of the etiology of FCHL [38].

Regardless of the multiple factors that may influence the expression of dyslipidemia in the pediatric age group, results of universal lipid screening indicate that there are a significant number of children with elevated LDL-C (>130 mg/dL) [39]. Of 20,226 10-year-old fifth-grade preadolescent students in West Virginia, a total of 71.4% of children met National Cholesterol Education Program (NCEP) guidelines for cholesterol screening on the basis of positive family history. Of those, 1204 (8.3%) had an elevated LDL-C >130 mg/dL, and 1.2% of these children had a dyslipidemia that warranted possible pharmacologic treatment (LDL-C >160 mg/dL) [39]. Of the 28.6% who did not have a positive family history (using NCEP guidelines), 548 (9.5%) had an LDL-C >130 mg/dL, 1.7% of whom warranted pharmacologic treatment. The panoply of fundamental defects causing LDL-C >160 mg/dL are not known at this time. Those with FH and defects in the LDLR can be distinguished from those with FCHL and hyperTG hyperapoB in whom the fundamental defects are not known. Clearly, a comprehensive screening assessment is important to identify those with elevated LDL-C, so appropriate hygienic measures or, in some cases, drug therapy may be instituted.

Genetics of FCHL FCHL accounts for up to 20% of premature CAD. Despite this, the identification of single gene defects underlying FCHL has remained elusive [38]. Two major strategies have been used to dissect the complex genetic background of FCHL, the candidate-gene and the linkage approach. A rather extensive list of genes has been associated with FCHL or its phenotypic traits. Some genes affect the FCHL phenotype in many pedigrees, while others are expressed in only several kindreds. One approach is to integrate these individual genes into common metabolic pathways such as adipocytes, production of hepatic fat and lipoproteins, and clearance of apoB-containing lipoproteins [38]. The adaptation of new traits beyond the lipid traits may identify novel pathways in FCHL. For example, variations of the activity or the expression of various nuclear factors (upstream stimulatory factor 1, USF1; transcription factor 7-like 2, TCF7L2; Hepatocyte nuclear factor 4 alpha, HNF4 alpha) [40], which regulate the expression of multiple genes involved in the metabolism of lipids or carbohydrates, may have a major role in the pathophysiology of FCHL.

Acylation-stimulating protein (C3adesArg/ASP) is an adipokine that acts on its receptor C5a anaphylatoxin chemotactic receptor (C5L2) to stimulate TG synthesis in adipose tissue [41]. A defect in ASP-mediated TG synthesis was previously described in a subset of hyperapoB/FCHL subjects. One of the 61 unrelated proband had a heterozygous variant (c.G968T) in C5L2, resulting in p.Ser323lle substitution in the carboxyl terminal region [42]. Eight family members of the proband were identified with one altered (±) C5L2 allele. Nine other family members had the wild-type (+/+) C5L2 sequence. The abnormal allele was associated with increased plasma TG, TC, LDL-C, apoB, and ASP. In cell-based ASP bioactivity assays, those with C5L2 (±) variant ($n=2$) had a 50% reduction in ASP-stimulated TG synthesis, glucose transport, and marked reduction in maximal binding (B(max)) [42]. By contrast, those with normal C5L2 alleles (+/+) responded normally. The p.Ser323Ile variant may alter C5L2 function and might be one molecular defect contributing to FCHL.

Treatment of Disorders of VLDL Overproduction Youth with the VLDL overproduction syndrome are likely to be insulin resistant, and a low-fat, high-carbohydrate diet typically has an adverse effect on the combined dyslipidemia lipoprotein profiles, often increasing TG, decreasing HDL-C, and increasing the total num-

ber of LDL particles. Consequently, a moderate low-fat diet in which simple carbohydrates are significantly decreased (low glycemic index) and unsaturated fatty acids replace saturated fatty acids is recommended [1, 2]. Affected children are often overweight or obese presenting a difficult problem to treat. Without some form of regular supervised aerobic exercise, at least every other day for 1 h, it is usually a significant challenge to optimize the lipoprotein profile.

The goal is to avoid the use of medications in youth with elevated TG, low HDL-C, and increased LDL particles. Patients with serum TG exceeding 500 mg/dL deserve more attention. Some children and adolescents will respond significantly to diet, aerobic exercise, and weight loss or weight control. Many will not. ω-3 Fish oils can be used in a dose of two 1-g capsules with breakfast and dinner (4 g per day). A 50% reduction in TG may be achieved but the response is pleiotrophic, especially if the diet is not strict [1, 2].

In regard to LDL, a child with FCHL 10 years of age or older may have an LDL-C >160 mg/dL (Table 5.1) and an elevated apoB, indicating a sufficiently elevated number of LDL particles to warrant treatment with a statin in those with a family history of premature CAD [1, 2].

Disorders of LDL Metabolism in Children and Adolescents Due to *Decreased* Production of VLDL/IDL/LDL: Disorders of *Reduced* LDL-C Levels

Abetalipoproteinemia

Abetalipoproteinemia is a rare, autosomal recessive disorder characterized by fat malabsorption, acanthocytes, and hypocholestrolemia in *infancy* [3, 43, 44]. Later in life, deficiency of fat-soluble vitamins leads to atypical retinitis pigmentosa, posterior column neuropathy, myopathy, and coagulopathy [3, 59, 60]. Fat malabsorption in infancy is associated with symptoms of failure to thrive (poor weight gain and steatorrhea) and lipid vacuoles invading enterocytes, which are visible on intestinal biopsy. Fat malabsorption is due to the inability to assemble and secrete chylomicrons from enterocytes. Symptoms of neurological problems begin during adolescence and include: dysmetria, cerebellar ataxia, spastic gait, and axonal peripheral neuropathy mimicking vitamin E malabsorption or Friedreich ataxia [3, 43, 44]. Anemia and arrhythmias may also present.

TC levels are exceedingly low (20–50 mg/dL). Total plasma apoB (apoB-48 and apoB-100) is undetectable, and thus the apoB-containing lipoproteins, i.e., chylomicrons, VLDL, IDL, and LDL, are absent. HDL levels are measurable but low. Vitamin E levels are extremely low. Parents of affected children have normal lipid levels.

The absence of plasma apoB was initially believed to be due to defects in *APOB*. However, the defect in synthesis and secretion of apoB-containing lipoproteins was found to be secondary to absent MTP, which normally permits the transfer of lipid to both apoB-48 and apoB-100 [3, 43, 44]. MTP is a heterodimer composed of the ubiquitous multifunctional protein, protein disulfide isomerase, and a unique 97-kDa subunit. Abetalipoproteinemia is caused by mutations that lead to the absence of a functional 97-kDa subunit.

Treatment of Abetalipoproteinemia The intake of fat is first reduced to 5–20 g/day to control steatorrhea, a step that results in marked clinical improvement and growth acceleration. The diet should also be supplemented with linoleic acid (e.g., 5 g corn oil or safflower oil/day). MCT as a caloric substitute for long-chain fatty acids may produce hepatic fibrosis, and thus MCT should be used with caution [3, 44, 45]. However, some children respond to MCT oil and/or fish oils [45]. Fat-soluble vitamins should be added to the diet. High-dose oral vitamin E (150–200 IU/kg/day) is essential to prevent or ameliorate neurologic and retinal complications. Vitamin E levels increase on treatment but remain low. Rickets can be prevented by normal quantities of vitamin D, but high doses of vitamin A (200–400 IU/kg/day) may be required to raise the level of vitamin A in plasma to normal. Enough vitamin K (5–10 mg/day) should be given to maintain a normal prothrombin time.

Table 5.2 Acceptable, borderline, and high plasma lipid, lipoprotein, and apolipoprotein concentrations for children and adolescents

Category	Acceptable	Borderline	High[1]	Low[1]
TC	<170	170–199	≥200	
LDL-C	<110	110–129	≥130	
Non-HDL-C	<123	123–143	≥144	
apoB	<90	90–109	≥110	
TG				
– 0–9 years	<75	75–99	≥100	
– 10–19 years	<90	90–129	≥130	
HDL-C	>45	35–45		<35
apoA-I	>120	110–120		<110

apoA apolipoprotein A, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *TC* total cholesterol, *TG* triglycerides

All values are in mg/dL. Values for plasma lipid and lipoprotein levels are from the National Cholesterol Education Program (NCEP) Expert Panel on Cholesterol Levels in Children [93]. Non-HDL-C values from Bogalusa are equivalent to NCEP Pediatric Panel cutoff points for LDL-C [124]. Values for plasma apoB and apoA-I are from the National Health and Nutrition Examination Survey III (NHANES III) [126]. [1]The cutoff points for a high or low value represent approximately the 95th and 5th percentiles, respectively [93, 124, 126]. For HDL-C and apoA-I, the tenth percentiles are 40 and 115 mg/dL.

Hypobetalipoproteinemia

The phenotype of hypobetalipoproteinemia (hypobeta) is characterized by notably low levels of LDL-C and apoB, usually defined as less than the lower fifth percentile (Table 5.2). TC is low; VLDL-C and TG are low or normal. Hypobetalipoproteinemia can be primary, or secondary to anemia, dysproteinemias, hyperthyroidism, and intestinal lymphangiectasia with malabsorption, myocardial infarction, severe infections, and trauma.

Familial Hypobetalipoproteinemia Familial hypobetalipoproteinemia is inherited as an autosomal dominant disorder. The mutations occur in *APOB* but not exclusively so. Affected individuals are usually asymptomatic, the prevalence of CVD is quite low, and longevity is often found. Those with a defect in *APOB* have decreased synthesis of apoB and reduced secretion of VLDL from liver, which can lead to about a threefold increase in hepatic fat. A relatively large number of mutations in *APOB* cause familial hypobetalipoproteinemia [46]. Almost all of the mutations are either nonsense or frameshift mutations that create a premature stop codon and a truncated apoB. Familial hypobetalipoproteinemia has also been linked to a susceptibility locus on chromosome 3p21, and in some families is linked neither to APOB nor to chromosome 3p21 [46].

Familial Combined Hypolipidemia Musunuru and colleagues [47] reported that two nonsense mutations in the angiopoietin-like 3 gene (*ANGPTL3*) on chromosome 4 resulted in markedly decreased LDL-C that was accompanied by notably low TG and HDL-C, a phenotype they termed familial combined *hypolipidemia*. LDL-C and TG levels were inherited as codominant traits while the low HDL-C was only present in the compound heterozygous patients. This novel finding in this large family suggests a new mechanism for decreasing LDL-C in patients.

Loss-of-Function Mutations in PCSK9 The phenotype of hypobetalipoproteinemia is also found in those with a loss-of-function mutation in the PCSK9 gene [5, 6]. In this case, the low LDL results not from decreased production of VLDL but from enhanced LDLR activity due to the decreased PCSK9 function [5, 6] (see also above). Patients with this cause of familial hypobeta also have a considerable lifelong reduction in CVD [48].

Homozygous Hypobetalipoproteinemia

The clinical phenotype of children with homozygous hypobetalipoproteinemia depends upon whether they are homozygous for null alleles in *APOB* (i.e., make no detectable apoB) or homozygous (or compound heterozygotes) for other alleles, which produce lipoproteins containing small amounts of apoB or a truncated apoB [49]. Null-allele homozygotes are similar phenotypically to those with abetalipoproteinemia including fat malabsorption, neurologic disease, and hematologic abnormalities as their prominent clinical presentation; they require similar treatment. However, the parents of these children have low LDL-C levels in contrast to parents of children with abetalipoproteinemia, who are normolipidemic.

Chylomicron Retention Disease

Chylomicron retention disease (CRD) or Anderson's disease is a rare genetic condition that causes malnutrition, failure to thrive, growth failure, and vitamin E deficiency, among other complications [50, 51]. The diagnosis is suspected based on a phenotype of chronic diarrhea with fat malabsorption and very low, but not absent LDL-C and apoB. In contrast to abetalipoproteinemia and homozygous hypobetalipoproteinemia, TG are normal in CRD [51]. Fat-laden enterocytes and vitamin E deficiency are invariably present and hepatic steatosis is common. Muscular complications include increased creatine kinase (CK) levels and cardiomyopathy. Ophthalmologic and neurological complications in CRD are less severe than in other types of familial hypobetalipoproteinemia; for example, there is little acanthocytosis and no retinitis pigmentosa. CRD is due to mutations in *SAR1B*, leading to a defective Sar1b protein, which prevents the transport of prechylomicrons from the endoplasmic reticulum to the Golgi apparatus [51]. No postprandial chylomicrons or apoB-48 are detected. Dietary treatment is critical because when a low-fat diet supplemented with lipid soluble vitamins (A and E) and essential fatty acids, is implemented normal growth resumes with reduction of gastrointestinal symptoms. Departure from a low-fat diet produces a rapid relapse and recurrence of symptoms. Essential fatty acid deficiency is especially severe early in life and requires especially large amounts of vitamin E to prevent neurological complications.

Disorders of TG Metabolism in Children and Adolescents Due to *Decreased* Catabolism of TG-Rich Lipoproteins.

Disorders of Exogenous Hypertriglyceridemia

In patients with severe hypertriglyceridemia in lipid clinics, most have severely deficient LPL activity [52]. Mutations in *APOC2,* glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (GPIHBP1), and *APOA5* are rare but the associated clinical phenotype is severe [52]. LPL and GPIHBP1 defects present in childhood while apoC-II and apoA-V defects usually present in adults.

Defective or Missing Lipoprotein Lipase LPL deficiency is a rare autosomal recessive disorder that causes profound hypertriglyceridemia (as high as 10,000 mg/dL), due to massive increases in chylomicrons and the inability to clear dietary fat [3, 43]. Because CM replace water (volume) in plasma, sodium levels artifactually decrease between 2 and 4 meq/L for each 1000-mg/dL increase of plasma TG [3]. Marked hypercholesterolemia, e.g., 300–1000 mg/dL, is usually also present, secondary to the hyperchylomicronemia; the child will have a ratio of TG to TC of at least 5 and usually 10. VLDL-C is normal, and HDL-C and LDL-C are low.

Obligate heterozygous parents of affected children are often consanguineous and have normal lipid levels, or a moderate hypertriglyceridemia. To date, more than 80 mutations in the LPL gene have been reported [43]. Missense mutations predominate in the LPL gene, with a preferential location in exons 3, 4, and 5, and in the catalytic triad, Asp_{156}, His_{241}, and Ser_{132}.

The diagnosis of LPL deficiency requires a determination of postheparin lipolytic activity (PHLA) [3]. The intravenous injection of heparin (60 U/kg) releases the membrane-bound lipases into the bloodstream. Total and HL lipolytic activity are determined and the LPL activity calculated as the difference. HL activity is normal and LPL activity markedly decreased. The level of apoC-II is normal, as judged by immunochemical methods.

The disorder usually presents early in the first year of life. Creamy blood is often noted in a hematocrit tube or when blood is drawn. Abdominal pain is common, presenting as colic in the infant or as an acute abdominal condition later in childhood. Other clinical features may include eruptive xanthomas, hepatosplenomegaly, and lipemia retinalis. Premature atherosclerosis does not occur in LPL deficiency since the chylomicrons are too large to enter the vascular wall to be atherogenic.

Defects in apoC-ll Hypertriglyceridemia can range from 800 to almost 10,000 mg/dL in a patient with a deficiency of apoC-II. Elevated chylomicrons may be expressed alone or accompanied by increased VLDL [3, 43]. TC can also be normal or increased (about 150 to 1000 mg/dL). The LDL and HDL-C levels are below the fifth percentile of normal persons (Table 5.2). This autosomal recessive disorder is rare. Abnormalities of the apoC-II gene are caused by either small deletions or splice-site mutations [3, 43].

LPL activity is absent or very low. apoC-II is present in only trace amounts. Addition of apoC-II to plasma of these patients in vitro, or by blood or plasma transfusion in vivo, restores normal PHLA activity. The problem usually presents in adulthood with pancreatitis, although one homozygote developed pancreatitis at the age of 6 years.

Defective GPIHBP1 GPIHBP1 is anchored in endothelial cells and "picks up" LPL from interstitial spaces and shuttles it across endothelial cells to the capillary lumen [53]. When GPIHBP1 is absent, hypertriglyceridemia can be severe. In addition, mutations in either GPIHBP1 or LPL that affect the ability of either to bind to *each other* can cause hypertriglyceridemia [53]. PHLA is very low.

Reduced apoA-V Levels of apoA-V are negatively correlated with TG. apoA-V may normally stimulate proteoglycan-bound LPL at the endothelium of capillaries [54]. Despite its low concentration in plasma (~150 ng/ml), apoA-V modulates lipoprotein metabolism by binding to GPIHBP1, an interaction that effectively localizes TG-rich lipoproteins in the vicinity of GPIHBP1's other ligand, LPL [55]. A number of molecular variants in apoA-V are associated with low apoA-V and higher TG levels; the aggregation of five variants can be associated with TG of >1000 mg/dL [43].

Treatment of Profound Exogenous Hypertriglyceridemia Treatment of profound exogenous hypertriglyceridemia requires a stringent restriction in fat to 10–15 g/day. (See also above.) Intake of linoleic acid must be maintained as 1% of the calories. With severe hyperchylomicronemia, medium-chain triglycerides (MCT), which are absorbed directly through the portal vein, can be added to the diet as 15% of calories. MCT can increase compliance to the strict low-fat diet and often lower TG to a greater extent than expected. A subset of LPL-deficient patients with unique, possibly posttranscriptional genetic defects respond to therapy with MCT oil and ω-3-fatty acids by normalizing fasting plasma TG; a therapeutic trial with MCT oil and fish oils should, therefore, be considered in patients with LPL deficiency [3, 4]. Standard lipid-altering drugs such as statins, fibrates, and niacin are ineffective in LPL, apoC-II and GPIHBP1 deficiency.

Disorders of Endogenous Hypertriglyceridemia

Together, more than 20% of the susceptibility to hypertriglyceridemia now is accounted for by common and rare genetic variants [55]. Previously, the classical Fredrickson hypertriglyceridemic phenotypes (I, IIb, III, IV, and V), once considered to be distinct based on biochemical features, now

have a shared genetic architecture. Thus, the use of the phenotypes has been avoided since they are nonspecific for genotypes.

Familial Hypertriglyceridemia (FHT) In some families, plasma TC, LDL-C, and apoB levels are normal, and chylomicrons are absent but VLDL-C and TG levels are elevated (>95th percentile, Table 5.2). This phenotype can occur in dyslipidemic children from such families. FHT is distinguished from FCHL by showing that the affected parent and siblings of the proband have *both* normal LDL-C and apoB levels, in contrast to FCHL, where LDL-C is borderline high or elevated and apoB or LDL-P is significantly increased. VLDL particles in FHT and FCHL are both TG-enriched; however, VLDL and apoB are being overproduced in FCHL, while in FHT VLDL are not being overproduced but the hydrolysis of their TG are decreased abnormally. The basis for such slower hydrolysis of TG may be related to common genetic variants in LPL while the rarer genetic variant is not present. Adults with FHT manifest glucose intolerance, obesity, hyperuricemia, peripheral vascular disease (PVD), and to a lesser extent CVD. FHT may be inherited as an autosomal dominant trait with delayed expression [55].

Disorders of Endogenous and Exogenous Lipoprotein Transport Dysbetalipoproteinemia (Type III Hyperlipoproteinemia)

Adults with dysbetalipoproteinemia present with elevations in both TC and TG, usually but not always, above 300 mg/dL. The hallmark of the disorder is the presence of VLDL that migrate as beta lipoproteins (β-VLDL), rather than prebeta lipoproteins (dysbetalipoproteinemia). β-VLDL reflects the accumulation of cholesterol-enriched remnants of both hepatic VLDL and intestinal chylomicrons (Fig. 5.1) [56]. These remnants result from the presence of a dysfunctional apoE, the ligand for the receptor-mediated removal of both chylomicron and VLDL remnants by the liver.

Premature atherosclerosis of the coronary, cerebral, and peripheral arteries in adults is often present. Xanthomas are common, especially planar lesions in the creases of the palms, and tuberoeruptive xanthomas over the knees or buttocks. Occasionally, tuberous and tendon xanthomas are found. Hyperuricemia and glucose intolerance occur in up to half the patients with this syndrome.

Human apoE exists as three major isoforms (E2, E3, and E4), each of which is specified by an independent allele at the locus for the apoE gene [56]. One in 100 persons is homozygous for the apoE2 allele, which results in decreased affinity of the TG-enriched remnants to their hepatic receptors; however, because the prevalence of this disorder is only 1:10,000, other modifying factors such as hypothyroidism, low-estrogen state, obesity, or diabetes are necessary for full-blown clinical expression. This recessive form of dysbetalipoproteinemia has a delayed expression beyond childhood.

In summary, the diagnosis of dysbetalipoproteinemia is based on: (1) demonstration of E2E2 genotype, (2) the presence of β-VLDL, and (3) a cholesterol-enriched VLDL (VLDL-C/TG ratio >0.30). LDL-C and HDL-C levels are low or normal [56].

Dysbetalipoproteinemia in Children and Adolescents A dominant form of dysbetalipoproteinemia is caused by one of several rare variants of apoE that usually involve the substitution of neutral or acidic amino acids for basic ones in the region of apoE that interacts directly with the LDLR [56]. The dominant form can be expressed in childhood and does *not* require the presence of modifying factors. Affected adolescents often present with yellow creases in their palms (planar palmar xanthomas). The diagnosis of this rarer form of dysbetalipoproteinemia will require partial sequencing of the apoE gene.

Treatment Children or adults with dysbetalipoproteinemia are very responsive to a low-fat, low-cholesterol diet that decreases the burden of TG-enriched remnants. Fibric acid derivatives

have traditionally been the treatment of choice, which normalizes both the TC and TG levels. Niacin and statins are also quite effective.

HL Deficiency Patients with HL deficiency can present with features *similar* to type III dyslipoproteinemia, including hypercholesterolemia, hypertriglyceridemia, accumulation of TG-rich remnants (including β-VLDL), planar xanthomas, and premature CVD [57]. Recurrent bouts of pancreatitis have been described. HL is homologous to LPL and pancreatic lipase. HL hydrolyzes TG and phospholipids in lipoproteins and normally converts IDL to LDL and large HDL_2 to HDL_3. In HL deficiency, therefore, LDL-C is usually low and HDL-C is often quite *high* (despite the hypertriglyceridemia).

HL deficiency is rare and inherited as an autosomal recessive trait. Obligate heterozygotes are normal. The diagnosis is made by a PHLA test to determine that HL activity is absent but LPL activity is normal. The molecular defect leading to severe HL deficiency has been reported in a Québec-based kindred. In the proband and two of her brothers, very low to undetectable HL activity resulted from compound heterozygosity for two rare HL gene (*LIPC*) mutations, a previously unknown missense mutation in exon 5 designated p.A174T and the previously reported p.T383M mutation in exon 8 of the HL gene [58].

Treatment includes a low-total-fat diet. In one report, the hypercholesterolemia and hypertriglyceridemia in HL deficiency improved dramatically on treatment with lovastatin, while gemfibrozil reduced TG but elevated LDL-C [57].

Treatment of More Severe Combined Exogenous and Endogenous Hypertriglyceridemia Treatment of the combined exogenous/endogenous TG disorders, including HL deficiency, starts with a fat-restricted diet, reduction to ideal weight, and, when necessary, drug therapy including the fibrates, ω-3 fatty acids, niacin, and the statins (see steps 1, 4, 5, 6; Fig. 5.1). Unlike the disorders of exogenous TG metabolism, the combined TG disorders of both exogenous and endogenous TG metabolism will respond to combined treatment with fibrates, fish oils, or niacin, which can often lower TG about 50%.

Familial Disorders of HDL Metabolism

The most common cause of the phenotype of low HDL-C levels (hypoHDL) is arguably secondary to VLDL overproduction, and the subsequent expression of hypertriglyceridemia, increased small LDL particles, and low HDL-C [59]. A number of *primary* HDL disorders include: familial hypoalphalipoproteinemia (hypoalpha) [60, 61]; homozygous gene deletions or nonsense mutations in apoA-I [60, 62]; missense mutations in apoA-I [60, 63]; more than 100 common and rare variants in ABCA1, including the prototype Tangier disease [64, 65]; and lecithin–cholesterol acyl transferase (LCAT) deficiency [66].

At the other end of the spectrum, there are several familial disorders of HDL metabolism that present with *elevated* HDL-C levels (>95th percentile; Table 5.2) and reduced CVD. These include a deficiency in CETP [67, 68], and familial hyperalphalipoproteinemia (hyperalpha) [60, 62].

Apolipoprotein A-I Mutations

APOA1 exists on chromosome 11 as part of a gene cluster with *APOC3* and *APOA*4. Molecular defects in *APOA1* include gene inversions, gene deletions, and nonsense and missense mutations [60, 62]. Homozygous gene deletions or nonsense mutations are rare and exhibit little if any biosynthesis of apoA-I by the liver and intestine. The virtual absence of apoA-I is accompanied by marked decreases in HDL-C. Obligate heterozygotes, as well as the homozygotes, develop premature CVD. In addition to precocious CVD, homozygous children can manifest other clinical findings of peripheral cholesterol deposition, e.g., retinopathy, cataracts, and xanthomas. Missense mutations in *APOA1* have been described in kindreds with low HDL-C levels. However, the relationship to premature CAD is less clear [60, 62].

Tangier Disease Tangier disease is an autosomal recessive disorder in which HDL-C levels are extremely low and of an abnormal composition (HDL Tangier or T). HDL_T are chylomicron-like particles, which disappear when a patient consumes a low-fat diet [64, 65].

The classic findings in children with Tangier disease include enlarged orange yellow tonsils, splenomegaly, and a relapsing peripheral neuropathy. The orange tonsils reflect the deposition of beta carotene-rich CE in foam cells in the lymphatic tissue. Foam cells can also occur in skin, peripheral nerves, bone marrow, and the rectum. Mild hepatomegaly, lymphadenopathy, and corneal infiltration (in adulthood) may also occur.

APOA1 in Tangier patients is normal. The underlying defect is a deficiency in *ABCA1* [64, 65] (Fig. 5.1). The very low HDL-C is due to the lack of cholesterol efflux by the deficient ABCA1 to nascent HDL; this deficiency can be measured in fibroblasts from Tangier patients [64, 65]. Some but not all patients with Tangier disease have premature CAD in adulthood [64, 65]. Treatment with a low-fat diet diminishes the abnormal lipoprotein species.

LCAT Deficiency

LCAT is located on the surface of HDL particles, and transfers fatty acids from the sn-2 position of phosphatidylcholine (lecithin) to the 3-β-OH group on cholesterol. In this process, lysolecithin and esterified cholesterol are generated (α-LCAT). Esterification can also occur on VLDL/LDL particles (β-LCAT).

Both α- and β-LCAT activities are missing in patients with classic LCAT deficiency [66], a rare, autosomal recessive disorder. More than several dozen mutations have been described in *LCAT,* which is located on chromosome 16. The diagnosis is suspected in patients presenting with low HDL-C, corneal opacifications, and renal disease (proteinuria, hematuria). The ratio of plasma UC to TC is measured, with a result >0.7 diagnostic of LCAT deficiency.

In *fish eye disease,* only α-LCAT activity is absent. Patients present with corneal opacifications, but do not develop renal disease [66]. Variability in clinical presentations of fish eye disease, compared to LCAT deficiency, may be due to differences in total LCAT activity.

To date, there is no treatment of the primary defects. Patients usually die from renal disease, and atherosclerosis may be accelerated by the underlying nephrosis. Patients with LCAT deficiency, and other lipid metabolic disorders associated with renal disease, should be aggressively treated, including a low-fat diet. The secondary dyslipidemia associated with the nephrotic syndrome responds to statin therapy.

Cholesteryl Ester Transfer Protein Deficiency

The role of cholesteryl ester transfer protein (CETP) in atherosclerosis is not completely understood. CETP is upregulated in liver and peripheral tissues in response to either dietary or endogenous hypercholesterolemia. Elevated HDL-C due to complete deficiency of CETP was initially described in Japanese families [67]. Several mutations in *CETP* are known. The prevalence of CAD in CETP deficiency is not straightforward. Some patients develop CHD in spite of lower levels of apoB in CETP deficiency [67]. Thus, it has not been resolved whether a genetic CETP deficiency is an independent risk factor for CAD.

Due to its important role in modulating HDL levels, CETP inhibitors were developed to raise plasma HDL-C. However, many side effects, including increased death from CAD, attributed to interference with aldosterone metabolism, were found with the first CETP inhibitor (CP529, 414: torcetrapib) [68]. Another CETP inhibitor (dalcetrapib) produced a modest increase in HDL-C, but did not produce any decrease in CAD; no marked side effects were observed. Anacetrapib produced a significant increase in HDL-C and a decrease in LDL-C and lipoprotein (a) (Lp (a)). A clinical trial is ongoing to determine the effect of anacetrapib on reduction of CAD.

Scavenger Receptor Class B Type I Receptor Deficiency

Scavenger receptor class B type I (SR-BI) is a functional lipoprotein receptor that participates in the selective uptake of CE from HDL [69], LDL [70] and VLDL [71] and is regulated by a number of factors. One of its major functions is to mediate the uptake of CE from the core of these lipoproteins. Single-nucleotide polymorphisms (SNPs) in the *SCARB1* gene are significantly associated with HDL-C levels [72]. Certain SNPs in *SCARB1* are significantly associated with subclinical carotid atherosclerosis [73].

Deficiency of Endothelial Lipase

Endothelial lipase (EL) is a member of the TG lipase family of proteins that includes LPL and HL. EL is a product of *LIPG* and primarily hydrolyzes phospholipids with little TG lipase activity. EL hydrolyzes the lipids in HDL the most efficiently of all the lipoproteins, converting HDL from a larger to a smaller particle. Rare loss-of-function EL variants produce a higher HDL-C [74]. However, these variants did not mediate any decrease in CAD.

Elevated Lp (a)

Lp (a) consists of a glycoprotein, apo (a), covalently linked to apoB-100 of LDL through a disulfide bond [75]. Apo (a) is highly homologous to plasminogen but has no protease activity. Lp (a) levels are highly heritable and are almost entirely related to the apo (a) gene on chromosome 6q27. Lp (a) enters the vascular wall and promotes atherosclerosis through its CE content, and thrombosis through its inhibition of plasminogen activity on the surface of endothelial cells. Lp (a) also appears to bind oxidized phospholipids, which may promote inflammation [75]. The precise physiological function of Lp (a) is unknown but it is a causative risk factor for CVD [76]. Lp (a) is significantly elevated in a small but definite group of *children* who develop *either* hemorrhagic or thrombotic stroke, often without any other lipid abnormality, but who may also have other thrombotic risk factors [77].

Diagnosis and Treatment of elevated Lp (a) The best method for diagnosis of elevated Lp (a) is an enzyme-linked immunosorbent assay (ELISA) using a monoclonal antibody. The upper limit of normal is 75 nmol/L. Niacin and estrogen can effectively lower Lp (a) levels, while the statins and fibrates do not. Although clinical trial evidence is lacking regarding the benefit of specifically lowering Lp (a) on the prevalence of CVD, the recommended approach is to treat LDL-C more aggressively in patients with CVD who also have elevated Lp (a). A statin is used to reduce LDL-C to <100 mg/dL, at a minimum. Niacin can be added to reduce Lp (a) and to increase HDL-C. Treatment of children with elevated Lp (a) and stroke is a clinical judgment. My own approach is to use aspirin 81 mg/day and consider a statin if the child has a LDL-C >110 mg/dL, the 75th percentile.

Guidelines for the Clinical Evaluation and Treatment of Dyslipidemia in Children and Adolescents

Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents

The National Heart, Lung, and Blood Institute initiated development of cardiovascular health guidelines for pediatric care providers based on a formal evidence review of the science with an integrated format addressing all the major cardiovascular risk factors simultaneously [1, 2]. Evaluated risk factors included family history, age, nutrition/diet, physical inactivity, tobacco exposure, blood pressure, lipid levels, overweight/obesity, diabetes mellitus, predisposing conditions, metabolic syndrome, inflammatory markers, and prenatal factors. These guidelines are reviewed here but with a focus on dyslipoproteinemia and atherosclerosis. The Expert Panel's

Report [1, 2] may be consulted for more details about other evaluated risk factors.

The Expert Panel reviewed the evidence for lipid screening [1, 2], and considered selected lipid screening versus universal lipid screening. A primary objective for universal lipid screening was to detect youth with heterozygous FH who were at high risk for precocious CVD as adults if untreated.

Evidence Supporting Universal Screening for Heterozygous FH FH remains the clearest biologic and genetic model linking elevated levels of LDL in children to premature atherosclerotic events in adults. The first expert pediatric panel from the National Cholesterol Education Program (NCEP) [78] in 1992 recommended selective lipid screening of children with a family history of premature CVD or known hypercholesterolemia in a parent to detect children with FH at markedly increased risk of adult premature CAD. However, selective screening misses 30–60 % of children with FH who are at the highest risk of developing premature CVD [10, 79].

Wald et al. [80] performed a meta-analysis of 13 studies using 1907 FH cases and 16,221 controls to examine detection rates of FH (sensitivity) for specified false-positive rates (0.1, 0.5, and 1 %) in newborns and in five age groups 1–9, 10–19, 20–39, 40–59, and > or = 60 years. TC discriminated best between those with and without FH when they were between ages 1 and 9, when the detection rates with TC were 88 %, 94 %, and 96 % for false-positive rates of 0.1, 0.5, and 1 %. The results were similar with LDL-C. Screening newborns was much less effective. Once an affected child was identified, measurement of TC detected about 96 % of parents with the disorder.

Cascade screening is the process of searching for relatives with FH once an individual is diagnosed with FH [81]. Cascade testing is not a suitable method of population screening for FH, because a separate method of systematically identifying new FH index cases is required to achieve a reasonable level of FH detection in the population [81]. Such an alternative systematic method of identifying new cases could itself be the method of population screening [81].

If screening for children with FH is to be efficacious, there must be a safe and beneficial treatment. Because children with FH only respond to a stringent diet low in total fat, saturated fat, and cholesterol with an average 10 % fall in LDL-C, the effect of statins was examined in a number of randomized, placebo-controlled, clinical trials of 10- to 17-year-old FH children [82]. The statins lowered LDL-C impressively from 21 to 39 % in the different studies [82]. There were no serious side effects. Furthermore, Wiegman et al. [83] demonstrated that treatment of FH children, aged 8–17 years, randomized to 20 or 40 mg of pravastatin/day ($n = 104$) for 2 years, had regression of cIMT compared to those in the placebo ($n = 107$) group. This was the first evidence that treatment of children with FH with a statin produces a decrease in early, subclinical lesions of atherosclerosis. Further, "earlier is better" since those younger Dutch children treated at 8–11 years of age at baseline had significantly lower cIMT 5 years later than those treated at 12–18 years of age [84].

Additional Beneficial Effects of Universal Lipid Screening In addition to detecting 90 % or more of children with FH at 9–11 years of age, universal lipid screening has the potential to identify a larger group of children who have less marked oligogenic dyslipidemia, or dyslipidemia associated with obesity and the metabolic syndrome, and increased cIMT.

Prevalence of Abnormal Lipid Levels in US Children The National Health and Nutrition Examination Survey (NHANES) for 1999–2006 reported that the prevalence of abnormal lipid levels among youths aged 12–19 years was 20.3 % [85]. This prevalence varied by BMI; 14.2 % of normal-weight youths, 22.3 % of overweight youths, and *42.9 % of obese* youths had at least one abnormal lipid level. Among all youths, 32 % had a high BMI and therefore would be candidates for lipid screening under American Academy of Pediatrics (AAP) recommendations [86]. "Given the high prevalence of abnormal lipid levels among youths who are overweight and obese in this study, clinicians should be aware of

lipid screening guidelines, especially recommendations for screening youths who are overweight or obese" [85].

Clinical Implications of Obesity and Dyslipidemia in Youth Juonala and colleagues [87] pooled 4380 subjects from the CVD in Young Finns Study, the Childhood Determinants of Adult Health Study, the Bogalusa Heart Study, and the Muscatine Study, and showed that obesity during childhood strongly and significantly *predicted* the following outcomes in adults in their fourth decade: type 2 diabetes, hypertension, high LDL-C, low HDL-C, high TG, and high-risk cIMT. Analyses were adjusted for age, sex, height, length of follow-up, and cohort. Those who had a normal BMI ($N=2794$) in childhood and remained nonobese as adults, or those who were obese ($N=274$) in childhood but nonobese as adults did *not* have increased risk for lipid- and nonlipid CVD risk factors or elevated cIMT. Conversely, as adults, both those ($n=500$) who were overweight or obese in both childhood and adulthood and those ($n=812$) who had normal BMI in childhood but were obese had increased risk for CVD [87]. These data are impressive and further emphasize the importance of prevention since if an obese child became a nonobese adult, they did not have increased risk of CVD outcomes.

Evidence that Universal Lipid Screening Will Detect "High-Risk" Dyslipoproteinemic Children who Develop Significant Subclinical Atherosclerotic Lesions as Adults The lipid and nonlipid risk factors for cardiovascular (CVD) disease in adults are expressed in childhood [88]. Strong and internally consistent relationships exist between baseline lipid and nonlipid CVD risk factors in free-living populations of children and adolescents and the development in young adults of: (1) atherosclerotic postmortem lesions [89, 90], (2) cIMT (90^{th} percentile) [91], and (3) coronary calcium [92, 93]. It is now known that the lipid and nonlipid CVD risk factors predict adult carotid IMT beginning at 9 years of age [88]. Predictors of these lesions include higher LDL-C, lower levels of HDL-C, obesity, higher blood pressure levels, and cigarette smoking. Non-HDL-C (total cholesterol minus HDL-C), an index of the cholesterol carried by all the atherogenic apoB-containing lipoproteins, was also found to predict early atherosclerotic lesions in youth and young adulthood [94].

Evidence that Selective Lipid Screening Will Miss Dyslipoproteinemic Children who May Qualify for Drug Treatment of Elevated LDL-C Lipid screening for FH will also provide the opportunity of detecting those with less severe but nevertheless significant dyslipoproteinemia that benefit from modification of lifestyle and may warrant drug therapy. Ritchie et al. [95] assessed *selective* versus *universal* lipid screening in a general population of 20,266 fasting fifth-grade students in West Virginia. A total of 14,470 (71.4%) met NCEP 1992 Guidelines [78] for lipid screening based on a family history of CAD. Of those, 1204 (8.3%) had elevated LDL-C (≥130 mg/dL) and 170 (1.2%) of these 14,470 children warranted possible pharmacologic treatment (LDL-C ≥160 mg/dL). Of the 5798 (28.6%) who did *not* have a positive family history, 548 (9.5%) had elevated LDL-C and 98 (1.7%) had LDL-C ≥160 mg/dL, indicating consideration of pharmacologic treatment. Universal lipid screening identifies children with either a modest or more marked LDL-C, who are undetected by selective screening, missing the opportunity for hygienic treatment and pharmacologic therapy in those 2–3% who have more extreme LDL-C elevations.

Concerns About the Efficacy, Safety, and Cost of Universal Lipid Screening Opponents of universal lipid screening point out that there are no randomized placebo-controlled clinical trials of either intensive hygienic intervention or pharmacologic LDL lowering starting in youth at high risk for future CVD that demonstrate that treatment for *three or more decades* decreases *clinical CVD events in adulthood* [96]. Such a study would be of such magnitude and expense that it is unlikely to ever be accomplished. Some initial data from the UK are available, indicating that treatment of young adults with FH, age 20–39

years, with statins led to a substantial reduction in coronary mortality [97].

Estimates of the cost-effectiveness of identifying and treating patients with FH are highly favorable in health-care systems that can implement cascade screening based on index case identification of middle-age adults and genetic testing; for example, in the UK, the cost is about US$ 7000/quality-adjusted life year [98]. Although the additional costs of universal screening are not known, the benefits of earlier CVD prevention in high-risk individuals would be considerable as will cost savings, as statin costs are reduced as those medications go off patent [96].

Finally, there has been concern about the adverse effects of "labeling" a child as having a cholesterol problem or being obese [96]. In this regard, there are few if any data from a clinical trial. In The Dietary Intervention Study of Children, thousands of children aged 8–10 years were first screened in schools to detect those with a higher LDL-C (average 90th percentile). After being randomized into either a behaviorally based intervention group, or a usual care group, 3 years later both groups had extensive psychological testing. There were no adverse effects for children in the intervention group in terms of academic functioning, psychological symptoms, or family functioning [99]. There was no evidence for adverse effects of being labeled as having high LDL-C or for obtaining dietary advice.

Pediatric "Metabolic Syndrome"

There is no current consensus regarding the definition of the metabolic syndrome in youth. Cook et al. [100] proposed a definition from the third NHANES survey in those aged 12–17 years. The metabolic syndrome was considered present if three or more of these factors are present: (1) TG of 110 mg/dL or higher; (2) HDL-C of 40 mg/dL or lower; (3) waist circumference, at the 90th percentile or higher; (4) fasting glucose, 110 mg/dL or higher; and (5) blood pressure, at the 90th percentile or higher for age, sex, and height (the percentiles are those derived from NHANES) [100]. A BMI higher than the 95th percentile for age and gender has been proposed as an alternative to waist circumference [96].

Obesity, Dyslipidemia, and the Metabolic Syndrome Obesity plays a critical role in the development of dyslipidemia and the metabolic syndrome [102–106]. The severity of obesity and insulin resistance fuels the development of the metabolic syndrome. Acanthosis nigricans is often a sign of underlying insulin resistance. Elevated highly sensitive C-reactive protein and decreased adiponectin [102] are often present. Koskinen et al. [107] found that apoB, but not oxidized LDL or small LDL, was associated with metabolic syndrome in youth. Metabolic syndrome variables cluster from childhood to adulthood [103]. The metabolic syndrome in youth predicts adult metabolic syndrome, brachial artery distensibility, subclinical atherosclerosis, diabetes, and CVD two to three decades later but is no better than body mass index alone [104–106, 108].

Screening for Dyslipidemia in Pediatrics

For the reasons outlined above, each child 9–11 years of age optimally should have a TC, HDL-C, and non-HDL-C performed around their 10-year-old visit to their pediatrician or family practitioner. Each of these lipid parameters can be measured accurately in a *nonfasting state*. If the TC or non-HDL-C is elevated above the 95th percentile or the HDL-C is low below the 5th percentile, (Table 5.2), an appointment is made to obtain a follow-up fasted sample. A lipid profile including a TC, LDL-C, HDL-C, and TG is ordered. A normal result is a TC, LDL-C, TG, or non-HDL-C < 75th percentile, or a HDL-C > 25th percentile (Table 5.2).

The patient may have an elevated or borderline-elevated TC, LDL-C, and TG, or a low or borderline-low HDL-C (Table 5.2) [78], or some combination. The non-HDL-C is calculated as (TC − HDL-C = non-HDL-C). Similar percentiles and definitions are available for non-HDL-C (Table 5.2) [109]. Youth who present with one

Table 5.3 Causes of secondary dyslipidemia in children and adolescents

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

or more elevated apoB-containing lipoproteins and/or or low apoA-I-containing lipoproteins will require closer follow-up. Measurement of thyroid, liver, renal tests, and urinalysis (to rule out common secondary causes of dyslipidemia) is essential (Table 5.3). As many as 40 % of obese children may have a dyslipidemia usually characterized by high TG and low HDL-C [100]. In addition, those considered to have the metabolic syndrome will often have elevated or borderline non-HDL-C [110] (Table 5.2).

Well-standardized immunochemical methods are available for apoB and apoA-I measurements [111]. Cutoff points for apoB and apoA-I from the National Health and Nutrition Education Survey (NHANES) are used [111] (Table 5.2). Those with a low HDL-C and elevated TG but normal or borderline LDL-C (Table 5.1) should have an apoB measured. Or, the number of LDL particles (LDL-P) can be assessed by nuclear magnetic resonance (NMR) spectroscopy. If the apoB or LDL-P are elevated in such children (Table 5.2), then the child probably has FCHL. The complete dyslipidemic expression of FCHL is often delayed until adulthood, although elevated apoB or LDL-P may be the first expression of FCHL in adolescents and young adults [112]. apoA-I can be measured in a child with a low HDL-C to determine the severity of the phenotype.

Advanced lipoprotein testing has been used in clinical research studies to determine the subclasses of VLDL, LDL, and HDL in children and adolescents using NMR spectroscopy [113–116]. Guidelines derived from such methods for the diagnosis and treatment of dyslipidemia in youth are currently being developed.

Guidelines for Treatment of Dyslipidemia in Children and Adolescents

Dietary Therapy

Treatment and Follow-Up with Dietary Treatment

It is highly recommended that the following web site (http://www.nhlbi.nih.gov/guidelines/cvd_ped/index.htm) [2] be visited to review the nutritional information synthesized by the recent Pediatric Panel. The following overall summary

of the recommendations for a Child 1 diet are as follows.

Long-term follow-up studies demonstrate that subjects who were breast-fed have sustained CV health benefits, including lower cholesterol levels, lower BMI, reduced prevalence of type 2 diabetes, and lower cIMT in adulthood [1, 2].

Ongoing nutrition counseling has been effective in assisting children and families to adopt and sustain recommended diets for both nutrient adequacy and reducing CV risk [1, 2].

Within appropriate age- and gender-based requirements for growth and nutrition, in normal children and in children with dyslipidemia, intake of total fat can be safely limited to 30% of total calories, saturated fat intake limited to 7–10% of calories, and dietary cholesterol limited to 300 mg/d. Under the guidance of qualified nutritionists, this dietary composition has been shown to result in lower TC and LDL-C levels, less obesity, and less insulin resistance [1, 2].

Under similar conditions and with ongoing follow-up, these levels of fat intake may have similar effects starting in infancy. However, fats are important to infant diets due to their role in brain and cognitive development. Fat intake in infants less than 12 months of age should not be restricted without medical indication [1, 2].

The remaining 20% of fat intake should comprise a combination of *cis*-monounsaturated and polyunsaturated fats. Intake of *trans* fats should be limited as much as possible.

Between ages 1 and 2 years as children transition from breast milk or formula, milk reduced in fat (ranging from 2% milk to fat-free milk) can be used based on the child's growth, appetite, intake of other nutrient-dense foods, intake of other sources of fat, and risk for obesity and CVD.

Optimal intakes of total protein and total carbohydrate in children were not specifically addressed, but with a recommended total fat intake of 30% of energy, the Expert Panel recommends that the remaining 70% of calories include 15–20% from protein and 50–55% from carbohydrate sources [1, 2].

Plant-based foods are important low-calorie sources of nutrients including vitamins and fiber in the diets of children; increasing access to fruits and vegetables has been shown to increase their intake.

Reduced intake of sugar-sweetened beverages is associated with reduced obesity measures [1, 2].

Safety and Efficacy of Dietary Therapy in Infants, Children, and Adolescents Overall, the Child 1 diet in children appears safe and efficacious when performed under supervision. Medical and nutritional support is necessary to reinforce good dietary behaviors and ensure nutritional adequacy. The Special Turku Coronary Risk Factor Intervention Project for Children (STRIP) [117, 118] is a randomized, prospective low-saturated-fat dietary counseling program, starting at 7 months of age. Beneficial effects mediated in part by the diet-induced reduction in TC include improved insulin sensitivity at 9 years of age [119], enhanced endothelial function in 11-year-old boys, but not in girls [120], decreased obesity in girls [121], and reduction of overweight-related cardiometabolic risk factors in adolescents [122].

In the Dietary Intervention Study in Children (DISC), starting at ages of 8–10 years, healthy children with high LDL-C levels (average 130 mg/dL) were ascertained through cholesterol screening in six schools and randomized into an intervention group and a usual care group. The intervention group received an intense behavior-based dietary intervention while the usual care group ate a normal diet. At the end of 3 years the intervention group had small (3.2 mg/dL) but significantly lower mean LDL-C levels than the usual care group [123], despite a rather notable fall in LDL-C levels during adolescence in both study groups [124]. The low-fat, low-cholesterol diet in the intervention group was associated with normal growth and development [125]. The intake of calcium, zinc, vitamin E, and phosphorus were below average but adequate [125]. The Intervention diet was associated with lower blood pressure levels [126].

Dietary Supplement with Plant Sterols. The use of margarines (about two-three servings daily) high in either plant stanol esters [127, 128] or plant sterol esters [129] can reduce LDL-C an additional 10–15%, when added to a low-fat diet.

Table 5.4 Guidelines for use of pharmacologic agents to lower LDL-C in children and adolescents [93]

Risk factors for CVD	Post-dietary LDL-C level	LDL-C treatment goal
None	> or = 190 mg/dL	Minimum < 130 mg/dL
		Desirable < 110 mg/dL
	> or = 160 mg/dL	
(1) Positive family history for premature CVD, or		
		Minimum < 130 mg/dL
(2) Two or more other CVD risk factors		Desirable < 110 mg/dL

Water-soluble fiber [130] such as psyllium [131, 132] may also provide an additional 5–10 % lowering of LDL-C.

Effect of a Low-Fat Diet in Childhood on Future CVD in Adulthood That a low fat-diet in childhood will prevent CVD in adulthood has been inferred from epidemiologic and clinical trial studies in adults [1, 2].

For higher-risk children and adolescents, a more stringent diet, Child 2, is recommended.

Guidelines for Treatment of Dyslipidemia in Children and Adolescents

Pharmacological Therapy

When to Start Drug Therapy The primary use of lipid-altering drugs in pediatrics is to lower significantly elevated LDL-C [1–4] (Table 5.4). Drug treatment to lower LDL-C can be initiated at 10 years of age. The AAP [86] indicated that onset of treatment might be lowered to 8 years of age in children with marked elevations in LDL-C and a striking family history of premature CVD. This is related to the recent evidence that "earlier is better" in regard to producing the greatest regression of cIMT [84]. A more conservative approach is to wait to treat with drugs until Tanner stage II in males and after menstruation in girls but there is no evidence that statins affect sexual development.

Criteria for Instituting Drug Therapy Pharmacologic treatment of elevated LDL-C in youth can be considered if the post-dietary LDL-C is: (1) ≥ 190 mg/dL and there is a negative or unobtainable family history of premature CVD and no major CVD risk factors; or (2) ≥ 160 mg/dL and there is a family history of premature CVD or two or more risk factors for CVD are present [1–4, 78] (Table 5.4).

LDL-C Goals for Drug Treatment The minimum goal after drug treatment is a LDL-C < 130 mg/dL (Table 5.4). A desirable goal is a LDL-C < 110 mg/dL, which is below a borderline-elevated LDL-C of 110–129 mg/dL (Table 5.2).

HMGCoA Reductase Inhibitors (Statins)

The statins are generally the first class of drugs that are used to treat children 10–17 years of age with autosomal dominant hypercholesterolemia (FH, Defective apoB-100; FH3) or significant FCHL.

A meta-analysis of a number of randomized, placebo-controlled trials of the statins [82–84] showed good efficacy for lowering LDL-C and apoB from about 20 to 40 %, depending on the statin used. There was no major side effect in the children treated with the statins, compared with placebo [82–84]. Atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin, and rosuvastatin are approved by the FDA for use in children with FH 10–17 years of age. The equivalent potencies are about: 5 mg rosuvastatin = 10 mg atorvastatin = 20 mg simvastatin = 40 mg lovastatin = 40 mg pravastatin = 80 mg fluvastatin. Both atorvastatin

and rosuvastatin have long half-lives of about 17 h. Thus, they can be taken in the morning or evening, in contrast to the other statins, which should be taken at bedtime because of their short, half-lives. All statins except fluvastatin and rosuvastatin are available generically.

Efficacy of Statins on LDL-C Reduction: Consideration of Combined LDL-C-Lowering Agents The ability of the statins to achieve LDL-C goals (Table 5.4) will be related to how high the baseline LDL-C is elevated. In one study, the average baseline post-dietary LDL-C in FH heterozygotes was 232 mg/dL. When a higher dose of 20 mg of the most potent statin, rosuvastatin, was used, the mean LDL-C fell 50%, but still 40% of these FH children and adolescents did not achieve an optimal LDL-C goal of <110 mg/dL (a normal LDL-C level, Table 5.2) [133]. A second drug can be considered to take advantage of the complementary action on LDL-C reduction when either a BAS or ezetimibe is added to a statin. All three of these agents reduce hepatic cholesterol leading to an upregulation of LDLR activity. The effect of BAS and ezetimibe on increasing HMGCoA reductase activity is obviated by the concurrent use of a statin (Fig. 5.1). One can also avoid the use of the highest dose of one of the more potent statins. For example, ezetimibe was combined with simvastatin to affect an additional 15–25% decrease in LDL-C in FH heterozygous children [134]. There is also a nonlinear dose–response relation when a BAS or niacin is added to statin [135]. Combination of another LDL-C-lowering agent to a statin should be undertaken in consultation with a lipid specialist.

Effect of Statins on cIMT Wiegman et al. [83] found that a 24% reduction in LDL-C with pravastatin in FH heterozygotes 8–15 years of age significantly decreased cIMT compared with placebo. Younger age at statin initiation was an independent predictor of effect of treatment on cIMT in this Dutch study [84]. In an open label study in FH heterozygotes 10–16 years of age using fluvastatin 80 mg/day, median LDL-C fell 34% but there was no significant change in carotid IMT [136]. Early intervention with statins appears likely to reduce the risk of future atherosclerosis and CVD in those with FH.

Side Effects of the Statins in Children and Adolescents Statins are generally well tolerated, especially in youth, and have an excellent safety profile with minimal side effects. In a meta-analysis [82], the prevalence of elevated alanine amino transferase three times above the upper limit of normal (ULN) in the statin group was 0.66% (3 per 454). Instances of asymptomatic increases (>10-fold) in creatine kinase (CK), although unusual, have been reported in adolescents receiving statin therapy [82]. CK can also increase notably following several days of vigorous physical activity, which resolves spontaneously within a week. No cases of rhabdomyolysis have been reported [82, 133, 134].

Liver function tests (aspartate aminotransferase, AST; alanine transaminase, ALT) should be monitored at baseline, following 6–8 weeks after initiating treatment and every 4 months for the first year. After that, youth on a stable dose of a statin can have their liver function tests monitored every 6 months. Consideration should be given to reducing the dosage of drug, or its discontinuation, should the liver function tests exceed three times the upper limit of normal and remain there. CK should be measured at baseline and repeated if the patient develops muscle aches and cramps. The statin is discontinued if the CK is >5 times the upper limit of normal in those with symptoms of myositis, or >10 times the upper limit of normal in asymptomatic patients. In adults, 1/500 to 1/1000 patients may develop myositis on a statin, which can lead to life-threatening rhabdomyolysis [137]. Rhabdomyolysis is a rare event, occurring at an incidence of 1.2 per 10,000 patient-years [137]. Three statins, lovastatin, simvastatin, and atorvastatin, are metabolized by the CYP3A4 isozyme of the cytochrome P450 microsomal enzyme system, and consequently have drug interactions with other agents metabolized by CYP3A4. Examples include erythromycin, verapamil, cyclosporine, HIV protease inhibitors, sertraline, and the fibric acid derivative gemfibrozil. Larger intakes of grapefruit juice with these agents can also inhibit CYP3A4.

Special Issues in Young Females

The statins are effective and safe in adolescent girls, with no significant adverse effect on growth and development or on gonadal and adrenal hormones [82].

Because of the potential risk to a developing fetus, statins are contraindicated during pregnancy. Birth control is mandatory for those who are sexually active. Because of this concern, the long-term commitment to therapy, and the fact that risk of CAD increases after menopause, some specialists believe that statins should not be used to treat adolescent FH females. Others do recommend treatment of adolescent FH females, especially those with a striking family history of premature CAD. Additional studies are needed to document the long-term safety of statins and to determine their effects on future CVD.

Bile Acid Sequestrants (BAS)

BAS were the only class of drugs originally recommended by NCEP [78] for pharmacologic lipid-lowering therapy because of their long track record of safety over three decades. BAS do not enter the bloodstream, but bind bile acids in the intestine [138], preventing their reabsorption through the ileal bile acid transporter (IBAT) (Fig. 5.1). The decreased return of bile acids stimulates the conversion of cholesterol to bile acids through 7α-hydroxylase, lowering the hepatic cholesterol content and inducing LDL receptors (Fig. 5.1). The BAS produce a modest LDL-C reduction of about 10–15% [139–142]. The first-generation BAS, cholestyramine and colestipol, suffered from significant tolerability issues including constipation, heartburn, bloating, decreased serum folate levels, and interference with the absorption of other drugs [138]. In one study, over 80% of FH heterozygous children discontinued BAS after an average of 22 months, secondary to gritty taste and gastrointestinal complaints [141]. The second-generation sequestrant, colesevelam (625-mg tablets, three twice daily or six once a day), has a greater affinity for bile salts and can be used in a lower dose. Colesevelam is associated with less annoying side effects than cholestyramine, such as constipation and gritty taste. Colesevelam, alone or combined with a statin, is approved by the FDA as an adjunct to diet and exercise to reduce LDL-C in boys and post-menarchal girls, aged 10–17 years with heterozygous FH. Colesevelam can be administered as 625-mg tablets or as an oral suspension [142].

Safety of BAS In randomized clinical trials, cholestyramine did not affect height velocity [138–140]. Levels of fat-soluble vitamins were maintained, except that the BAS group had significantly lower 25-hydroxyvitamin D than the placebo group. Low-folate and high-homocysteine levels have been reported on BAS [139].

Cholesterol Absorption Inhibitor (CAI)

The CAI ezetimibe decreases the intestinal absorption of cholesterol derived from diet and from bile by about 50% through its high-affinity inhibition of NPC1L1 [143] (Fig. 5.1). This leads to a decrease in hepatic cholesterol, increased LDL receptor activity, and decreased LDL-C levels. NPC1L1 is localized at the brush border of enterocytes that normally moves cholesterol from mixed micelles into the cells of the jejunum [143] (Fig. 5.1). Ezetimibe lowers LDL-C by about 15–20% either alone or when combined with a statin [24, 139, 145]. Ezetimibe is not yet approved by the FDA for use in children, except in very rare cases of sitosterolemia [24] or homozygous FH [145]. While there have been isolated case reports of possible ezetimibe-associated myopathy, there is no evidence from randomized clinical trials of increased myopathy or rhabdomyolysis with ezetimibe [138]. Other side effects include gastrointestinal upset, headache, and increased incidence (about 3%) of elevated liver function tests when combined with a statin. Ezetimibe is administered in one dose only, 10 mg/day.

Niacin (Nicotinic Acid)

Niacin is not routinely used in pediatrics since there are few published data on its safety and efficacy of niacin in youth. The single exception is the FH homozygous patient (see above).

Fibrates

Fibric acid derivatives (fibrates) are agonists for the peroxisome proliferator-activated receptor alpha (PPAR alpha), which upregulate the gene for LPL and apoA-V, and downregulate the gene for apoC-III [147] (Fig. 5.1). Fibrates also upregulate the gene for apoA-I, which increases HDL-C levels. Use of a fibrate is usually reserved for that adolescent with fasting TG over 500 mg/dL, who may be at an increased risk of pancreatitis. The most common side effects of fibrates are upset stomach, nausea, or vomiting. Abdominal pain is the second most common side effect. There is a slightly increased risk of gallstones. Gemfibrozil can potentiate drugs that prevent blood clotting (anticoagulants), causing bleeding. Use of gemfibrozil with statins can potentiate myositis, myalgias, and rhabdomyolysis. Such combined therapy is used only in consultation with a lipidologist.

Fish Oils

Fish oils are enriched in eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). These ω-3 fatty acids inhibit the production of TG in liver by several postulated mechanisms, including interfering with the incorporation of FFA into TG (Fig. 5.1). Fish oil preparations concentrated with EPA and DHA can be used as prescription formulations, Lovaza and Vascepa. The prescription versions of ω-3 fatty acids are not yet approved by the FDA for use in children. TG can be significantly lowered in youth up to 25–50% at a dose of two 1-g capsules taken twice daily (4 g per day). Side effects are mostly gastrointestinal upset and a "fishy taste or smell" [1–4]. Fish oils should be kept refrigerated to minimize the fishy taste and odor.

Treatment of Dyslipidemia Secondary to Other Diseases [1–4]

Insulin Resistance Metformin has been used in several studies of obese adolescents with the metabolic syndrome and hyperinsulinemia to lower fasting plasma glucose and insulin [148, 149].

Type I Diabetes Youth with type I diabetes are at high risk for CVD as adults and already have increased cIMT [150]. After dietary therapy and the best achievable diabetic control, the American Diabetes Association strongly recommends the use of statins in those with LDL-C > 160 mg/dL and to consider it in those with a LDL-C > 130 mg/dL [150].

Nephrotic Syndrome The dyslipidemia in children with the nephrotic syndrome can be marked, with both TC and TG that approach 300 mg/dL or higher [151]. Those patients who are *unresponsive* to steroids and have a post-dietary intervention LDL-C of more than 160 mg/dL may be at an increased risk for CVD [151] and may warrant treatment with a statin, which is effective in this condition.

Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) presents in adolescent females with menstrual disorders, acne, and hirsutism [152, 153]. Insulin resistance and dyslipidemia are often present. After diet and weight control, an estrogen/progesterone combination is often used [152]. Metformin can be considered, especially in those who are obese. Increased cIMT is present in young adults with PCOS [152, 153], and treatment with a statin can be considered in those with LDL-C > 160 mg/dL.

Summary

This chapter covers the fundamental and practical aspects of dyslipoproteinemia in children and adolescents. Plasma lipoprotein metabolism germane to youth is examined. The inherited dyslipoproteinemias are discussed in sufficient detail to serve as a resource to support further diagnostic evaluations and treatment strategies in such children and adolescents. Finally, most youths seen by practitioners do not have an inherited dyslipoproteinemia but one that is influenced by oligogenic factors and affected by environmental contributors such as diet, physical inactivity, and obesity. A strong case is made for universal lipid screening between 9 and 11 years of age. Thus, there is a challenge to detect and treat children with both genetic and common dyslipoproteinemias as well. The practical section on diagnosis and treatment provides an integrated approach to dyslipoproteinemia.

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