Recognition and Management of Dyslipidemia in Children and Adolescents

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Context: Cardiovascular disease (CVD) remains the number one cause of death in the United States. The origins of atherosclerosis and CVD begin in childhood. Dyslipidemia and obesity are endemic in American youth and require urgent action.

Evidence Acquisition: A detailed literature search from 1985–2008 was performed using PubMed and subsequent reference searches of retrieved articles. Selection of included articles was based on rigor of scientific design, adequate sample size, quality of the data, statistical analysis, and hypothesis testing.

Evidence Synthesis: CVD risk factors in children predict pathological lesions of atherosclerosis in young adults, and their clinical manifestations, as judged by carotid intima medial thickness, coronary artery calcium, or brachial flow-mediated dilatation. About half the offspring of a parent with premature CVD have a primary dyslipidemia. However, use of family history to identify such youth will miss the majority of children with dyslipidemia. Treatment of dyslipidemia starts with a low-fat diet supplemented with water-soluble fiber, plant stanols, and plant sterols, weight control, and exercise. Drug therapy with inhibitors of hydroxymethylglutaryl coenzyme A reductase, bile acid sequestrants (BAS), and cholesterol absorption inhibitors can be considered in adolescents with a positive family history of premature CVD and a low-density lipoprotein cholesterol of more than 160 mg/dL. Such dietary and drug therapy appears safe and efficacious and is likely to retard atherosclerosis.

Conclusions: Early identification and treatment of youth at risk for early atherosclerosis will require an integrated assessment of predisposing CVD risk factors and a comprehensive universal screening and treatment program. **(*J Clin Endocrinol Metab* 93: 4200–4209, 2008)**

Early atherosclerotic lesions in children, adolescents, and young adults who died from accidental deaths are significantly related to higher antecedent levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C), lower levels of high density lipoprotein (HDL)-C, and other cardiovascular disease (CVD) risk factors, such as obesity, higher blood pressure levels, and cigarette smoking (1, 2). Four major prospective epidemiological studies from Muscatine (3, 4), Bogalusa (5), the Coronary Artery Risk Development in Young Adults (CARDIA) (6), and the Special Turku Coronary Risk Factor Intervention Project (STRIP) (7, 8) showed that CVD risk factors in children and adolescents, particularly LDL-C and obesity, predicted clinical manifestations of atherosclerosis in young adults, as judged by carotid intima medial thickness (IMT), coronary artery calcium, or brachial flow-mediated dilatation. Medical students at Johns Hopkins who had a TC higher than 207 mg/dl had five times the risk of developing CVD 40 yr later than those students who had a TC lower than 172 mg/dl(9).

In three studies, offspring of a parent with premature CVD had 1) one of seven dyslipidemic profiles, *i.e.* elevated LDL-C alone (type IIa) or combined with high triglyceride (TG) (type IIb), elevated TG alone (type IV), low HDL-C alone (hypo-α),

0021-972X/08/$15.00/0

Printed in U.S.A.

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doi: 10.1210/jc.2008-1270 Received June 12, 2008. Accepted August 4, 2008.

First Published Online August 12, 2008

Abbreviations: apoB, Apolipoprotein B; BAS, bile acid sequestrant; C, cholesterol; CAI, cholesterol absorption inhibitor; CAD, coronary artery disease; CVD, cardiovascular disease; FCHL, familial combined hyperlipidemial FH, familial hypercholesterolemia; HDL, high-density lipoprotein; HMG-CoA, hydroxymethylglutaryl coenzyme A; IDL, intermediate-density lipoprotein; IMT, intima medial thickness; LDL, low-density lipoprotein; LDLR, LDL receptor; PCOS, polycystic ovary syndrome; SREBP, sterol regulatory element binding protein; TC, total cholesterol; TG, triglyceride.

and type IIa, type IIb, or type IV also accompanied by low HDL-C (10); 2) hyper-apobetalipoproteinemia (hyper-apoB), *i.e.* elevated apolipoprotein B (apoB) but normal LDL-C (11); and 3) apoB and apoA-I levels that were stronger predictors of parental CVD than LDL-C and HDL-C (12). Inherited lipoprotein disorders that often present in youth at high risk of future CVD include familial hypercholesterolemia (FH), familial combined hyperlipidemia (FCHL), and hyper-apoB.

Screening for Dyslipidemia in Youth

The literature related to screening in the general *vs.* a selected population has been reviewed in detail (13).

Who to screen

Selective screening

The National Cholesterol Education Program (NCEP) Expert Panel on Blood Cholesterol Levels in Children and Adolescents (14) recommended in 1992 that selective, not general, screening be performed. I have expanded these recommendations (in italics) in the following NCEP guidelines for screening: 1) a lipoprotein profile in youth whose parents and/or grandparents required coronary artery bypass-surgery or balloon angioplasty before age 55; 2) a lipoprotein profile in those with a family history of myocardial infarction, angina pectoris, peripheral or cerebral vascular disease, or sudden death before age 55; 3) a TC in those whose parents have high TC levels (>240 mg/dl) (this recommendation might be usefully expanded to a lipoprotein profile in offspring of parents who have any dyslipidemia); 4) a lipoprotein profile if the parental/grandparental family history is not known, and the patient has two or more other risk factors for coronary artery disease (CAD) including obesity [body mass index (BMI) >30 kg/m^2], hypertension, cigarette smoking, low HDL-C, physical inactivity, and diabetes mellitus; and 5) a new recommendation for a specific category proposed: a lipoprotein profile if either obesity (BMI >95th percentile) or overweight (BMI 85–94th percentile) is detected *per se*, regardless of the presence of other nonlipid CVD risk factors. This recommendation is congruent with the recent guidelines from the American Academy of Pediatrics (15), namely that "overweight children belong to a special risk category of children and are in need of cholesterol screening regardless of family history or other risk factors."

Universal screening

Universal screening of all children for dyslipidemia is controversial (13, 14–16). What are the arguments that favor universal screening?

First, current screening recommendations based on family history of CVD or hypercholesterolemia will fail to detect substantial numbers (from 17–90%) of children who have elevated lipid levels (13). Many children with genetic disorders may also be missed by selective screening, especially if their parents are young, free of CVD, and unaware of their own lipid levels.

Therefore, universal screening might be performed to detect those with undiagnosed heterozygous FH or more marked FCHL, who will require more intensive treatment, including the possibility of drug therapy. In a recent metaanalysis of screening for FH in a primary care setting, use of TC detected 88–96% of cases, with false-positive rates of less than 1% (17). Ten years of age has been considered as a good age to screen (13, 16), before the effect of puberty lowers LDL-C levels but closer to an age when drug therapy may be appropriate.

The identification of hypercholesterolemic children by universal screening will bring to attention their adult relatives who will have greater coronary mortality than relatives of normocholesterolemic children (17, 18). If universal lipid screening is combined with an assessment of obesity and high blood pressure, this can also lead to the detection of additional relatives from families at high risk for CVD (19).

It is clear that CVD risk factors cluster in childhood and persist into adulthood (1–13, 20). Treatment with diet and hygienic measures and with medication can be effective (see also below).

Each child and adolescent should ideally have an assessment of their plasma lipids and lipoproteins. Although there are practical problems (see below), and no longitudinal studies are available to show that treatment starting in childhood decreases adult CVD (13), one might argue that universal screening seems all the more urgent, given the epidemic of obesity and the metabolic syndrome in American youth.

What are some of the concerns about universal lipid screening in childhood? A number of longitudinal studies (13) have found that when the 75th percentile for TC in children is used as a screening cutoff point, about half those who will require treatment as adults are identified by universal lipid screening. In one report, the sensitivity was much lower when screening occurred during adolescence, presumably reflecting the temporary downward shift of LDL-C during this period of rapid growth and development (1, 21, 22).

Another unresolved question is whether the detection of elevated TC or LDL-C in children and young adults will predict those adults destined to manifest premature CVD.

The American Academy of Pediatrics stopped just short of recommending universal screening. If universal screening for lipid and nonlipid CVD risk factors becomes the standard of pediatric care, national resources clearly will be required to detect and treat those found to be at increased risk of CVD.

What to measure

For selective screening, a lipoprotein profile is measured after an overnight fast. Such a profile includes TC, TG, LDL-C, HDL-C, and non-HDL-C. LDL-C is calculated from the Friedewald equation: LDL-C = TC − (HDL-C + TG/5). TG in the fasting state divided by 5 is used to estimate very-low-density lipoprotein (VLDL)-C. If TG is more than 400 mg/dl, this formula cannot be used, and a direct LDL-C may be measured. TC, HDL-C, and non-HDL-C can be determined nonfasting.

Well-standardized immunochemical methods are available for apoB and apoA-I measurements (23, 24), particularly in youth with premature CVD in parents (11, 12). Cutoff points for apoB and apoA-I from the National Health and Nutrition Education Survey (NHANES) are used (23) (Table 1).

TABLE 1. Acceptable, borderline, and high plasma lipid, lipoprotein, and apolipoprotein concentrations for children and adolescents

Category	Acceptable	Borderline	High[a]	Low[a]
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 yr	<75	75–99	≥100	
10–19 yr	<90	90–129	≥130	
HDL–C	>45	35–45		<35
ApoA–I	>120	110–120		<110

Values for plasma lipid and lipoprotein levels are from the National Cholesterol Education Program (NCEP) Expert Panel on Cholesterol Levels in Children (14). Non-HDL-C values from Bogalusa are equivalent to NCEP Pediatric Panel cutoff points for LDL-C (26). Values for plasma apoB and apoA-I are from the National Health and Nutrition Examination Survey III (NHANES III) (23).

[a] The cutoff points for a high or low value represent approximately the 95th and 5th percentiles, respectively (14, 23, 26).

Non-HDL-C

Non-HDL-C is determined by subtracting HDL-C from TC and reflects the amount of cholesterol carried by the atherogenic apoB-containing lipoproteins [VLDL, intermediate-density lipoprotein (IDL), LDL, and lipoprotein(a)]. In adults, non-HDL is a better independent predictor of CVD than LDL-C (24). In children, non-HDL-C is at least as good a predictor as LDL-C of future dyslipidemia in adulthood (1, 25). Percentiles for non-HDL-C in children are available from Bogalusa (26) (Table 1).

Advanced lipoprotein testing

The plasma levels of VLDL, LDL, and HDL subclasses have been determined in children and adolescents by nuclear magnetic resonance spectroscopy (27–29) or by vertical-spin density-gradient ultracentrifugation (30) in research studies (see also below), but cutoff points derived from these methods for the diagnosis and treatment of dyslipidemia in youth are not currently available.

Summary

For universal screening, the simplest approach is the measurement of TC, HDL-C, and non-HDL-C in nonfasting specimens. However, treatment algorithms in pediatrics are usually focused on fasting LDL-C. Hyper-TG is usually assessed as part of the dyslipidemic triad, obesity, and the metabolic syndrome (31–38). Ideally, a lipoprotein profile is obtained fasting.

When to sample for dyslipidemia

Human plasma cholesterol levels are lowest during intrauterine life and at birth (39). TC and LDL-C increase rapidly in the first weeks of life and then gradually until 2 yr of age. Screening for dyslipidemia is therefore generally recommended after 2 yr of age when the lipid and lipoprotein levels become quite constant up to adolescence (14).

Ten years of age has been proposed as a good time to obtain a lipoprotein profile (17). Children are older and able to fast easier, and results are predictive of future adult lipoprotein profiles and not subject to the 10–20% fall in TC and LDL-C that occurs during adolescence (21, 22). Even in FH adolescents, the decrement in LDL-C can produce a false-negative result (40). The complete dyslipidemic expression of FCHL can be delayed until adulthood, although elevated apoB is the first expression of FCHL in adolescents and young adults (41). A normal result in a high-risk adolescent will therefore need to be repeated at 18 yr of age.

Definition of dyslipidemia

Cutoff points to define elevated TC, LDL-C, apoB, non-HDL-C, and TG and low HDL-C and apoA-I in children and adolescents are found in Table 1. Dyslipidemia is present if one or more of these lipid, lipoprotein, or apolipoprotein levels are abnormal. In offspring of young progeny of men with premature CVD before 50 yr of age, seven different dyslipidemic profiles were present (10). Such results emphasize the importance of evaluating a lipoprotein profile in the fasting state.

Single vs. multiple cutoff points

Using data from three major population-based prospective cohort studies, TC, LDL-C, HDL-C, and TG variables in adolescence were classified according to NCEP cutoff points (14) (Table 1) and to age and gender (not race specific) NHANES cutoff points (42) and compared for their ability to predict abnormal levels in adulthood (43). NCEP cutoff points (compared with NHANES cutoff points) were more strongly predictive of high TC, LDL-C, and TG levels in adults but less predictive of low HDL-C (43). The continued use of the current NCEP cutoff points for TC, LDL-C, and TG levels in adolescents appears indicated. The cutoff point for HDL-C might be revised upward, perhaps to 40 mg/dl, to improve the sensitivity of this measurement to predict low HDL-C in adults and to make the cutoff point congruent with that used in adults.

Primary *vs.* Secondary Dyslipidemia

Secondary dyslipidemia

Before considering dyslipidemia primary, secondary causes must be excluded (Table 2). If dyslipidemia persists after treatment of the secondary disorder, the patient will require dietary and, if indicated, drug treatment (see below for guidelines).

Primary dyslipidemia

FH, FCHL, and hyper-apoB

The lipid, lipoprotein, and apoB levels found in the most common primary dyslipidemias associated with premature CVD are summarized in Table 3. FH is an autosomal dominant disorder due to defects in the LDL receptor (LDLR) gene (39, 40, 44, 45) (Fig. 1). FCHL (46, 47) and hyper-apoB (48–50) result from overproduction of VLDL, IDL, and LDL (Fig. 1). FCHL is at least 3-fold more prevalent than FH (50). The expression of FCHL can be delayed (46), but affected children with type IIa, IIb, or IV lipoprotein profiles (50) or isolated high apoB (41) can be detected in families with premature CAD (50). The precise defects in FCHL and

TABLE 2. Causes of secondary dyslipidemia in children and adolescents

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

hyper-apoB are unknown, but these disorders are probably oligogenic (51–57). A more detailed discussion of FH, FCHL, and hyper-apoB in youth can be found in several reviews (58, 59).

Rarer causes of dyslipidemias affecting LDLR activity

Rarer causes of dyslipidemia in youth associated with premature CVD and xanthomas include homozygous FH (44, 45), familial defective apoB-100 (FDB) (60), autosomal recessive hypercholesterolemia (ARH) (61, 62), sitosterolemia (63–65), and mutations in proprotein convertase subtilisin-like kexin type 9 (PCSK9) (66). Each disorder warrants diet and drug therapy (see below) in childhood in an attempt to decrease atherosclerosis and subsequent CVD.

Disorders of HDL metabolism

Most of the time, low HDL-C is secondary to VLDL overproduction (see above). Primary low HDL disorders include familial hypoalphalipoproteinemia (67, 68), apolipoprotein A-I mutations (67–70), common and rare variants in ABCA1 including Tangier disease (71), and lecithin cholesterol acyl transferase (LCAT) deficiency (72). One disorder, cholesteryl ester transfer protein deficiency, often presents as high HDL-C, but whether this is associated with increased or reduced risk of CVD is not resolved (73).

Disorders of TG metabolism

The inherited disorders of marked hyper-TG associated with pancreatitis such as lipoprotein lipase deficiency and defective apoC-II (58, 59) will not be reviewed here. Most hyper-TG in children is due to overproduction of VLDL (see also above). Rather, I will emphasize the paramount role of obesity and the metabolic syndrome in hyper-TG.

Definition of the metabolic syndrome

There is no current consensus regarding the definition of the metabolic syndrome in youth, and that in children ages 12–17 proposed by Cook *et al.* (32) from the third NHANES survey is one of several. An adolescent is considered to have the metabolic syndrome 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 or higher percentile, 4) fasting glucose of 110 mg/dl or higher, and 5) blood pressure at the 90th percentile or higher for age, sex, and height. One alternative to waist circumference may be a BMI higher than the 95th percentile for age and gender (74).

Obesity and the metabolic syndrome

Obesity is of critical importance in the development of the metabolic syndrome (31–37, 74–76). In the past 20 yr, the prevalence of adolescents with a BMI above the 95th percentile has increased by more than 50% (31). The prevalence of the metabolic syndrome increases with the severity of obesity and insulin resistance, as does the dyslipidemic triad, elevated highly sensitive C-reactive protein, and decreased adiponectin (34). Acanthosis nigricans is a sign of underlying insulin resistance. Higher LDL-C levels and obesity (5) and higher blood pressure levels (36) increase carotid IMT in adulthood. The metabolic syndrome in youth predicts adult metabolic syndrome and CVD two to three decades later (75, 76).

Guidelines for Treatment of Dyslipidemia in Children and Adolescents

Dietary therapy

Youth with dyslipidemia are first treated with a diet reduced in total fat, saturated fat, and cholesterol. The intake of complex carbohydrates is increased, whereas that of simple sugars is decreased. No decrease in total protein is recommended. Calories are sufficient to maintain normal growth and development. The NCEP pediatric panel recommended diet treatment after 2 yr of age (14). Recent data from STRIP (77–79) indicate that a low-fat diet may be instituted safely and effectively at 6 months of age under medical supervision.

TABLE 3. Levels of lipids, lipoproteins, and apoB in children with the most common lipoprotein abnormalities

Lipoprotein disorder	Age (yr)	Plasma concentrations (mg/dl)					
		TC	TG	HDL-C	LDL-C	ApoB	LDL-C/apoB
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
Hyper-apoB (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

Data are from Cortner *et al.* (50).

When to initiate treatment with diet

If the first lipoprotein profile indicates that TC, LDL-C, non-HDL-C, or TG is elevated or that the HDL-C is low (Table 1), then another profile is obtained at least 3 wk later to confirm the first profile. If the dyslipidemia persists, *i.e.* one or more of the lipid or lipoprotein values remains above the elevated cutoff point or HDL-C is low, secondary causes of dyslipidemia (Table 2) are ruled out and dietary treatment begun. A Step One diet is usually started

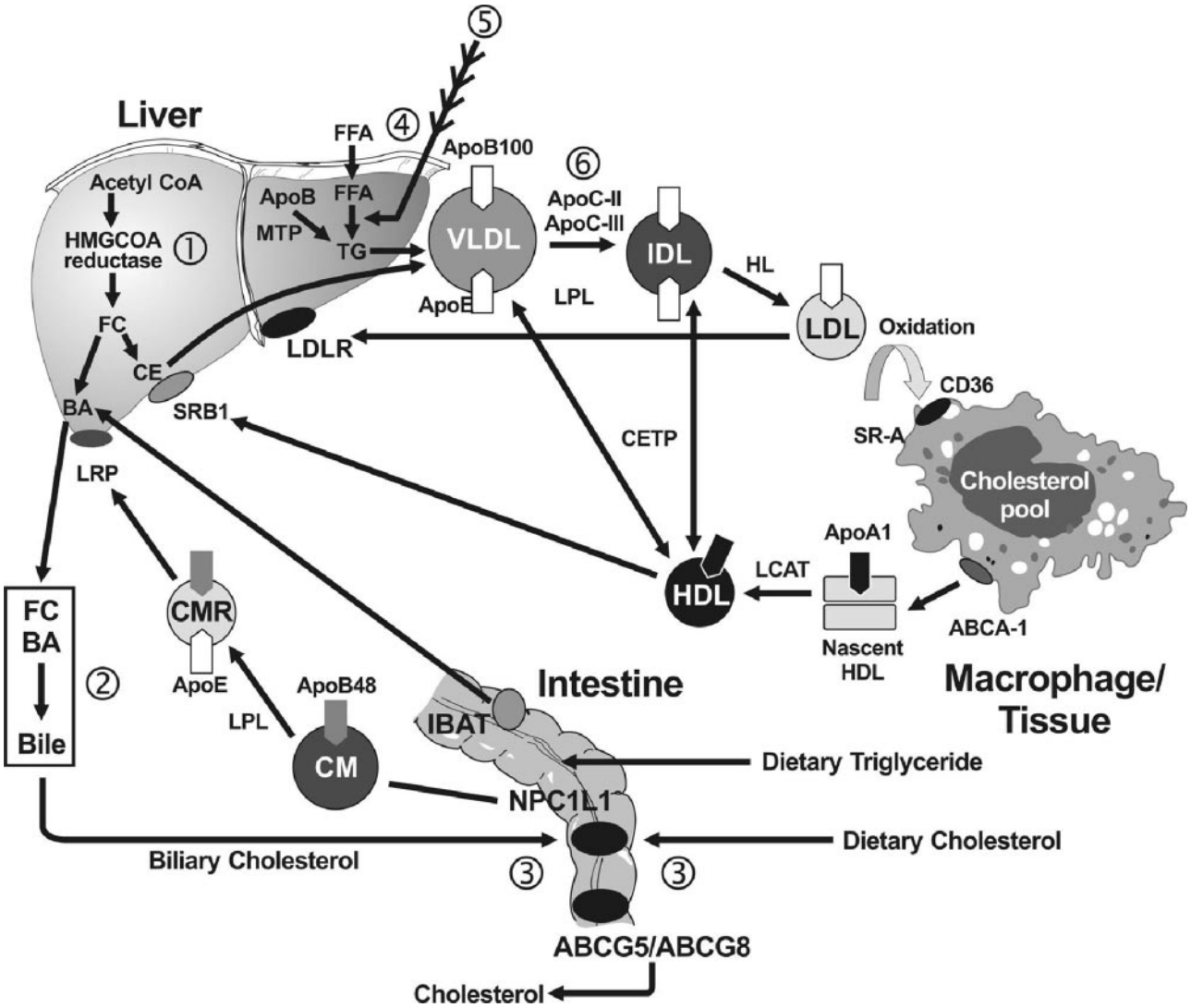

FIG. 1. Three major pathways of plasma lipoprotein metabolism are shown: 1) transport of dietary (exogenous) fat (*left*), 2) transport of hepatic (endogenous) fat (*center*), and 3) reverse cholesterol transport (*bottom*). Sites of action of the six major lipid-altering drugs on exogenous and endogenous pathways of lipoprotein metabolism are 1) inhibition of HMG-CoA 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 VLDL, IDL, and LDL production; 5) inhibition of TG synthesis by ω-3 fatty acids; 6) up-regulation 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 up-regulation 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.: *J Clin Lipidol*, in press (58). © Elsevier.]

and the lipoprotein profile repeated in 6–8 wk. If the dyslipidemia persists, then a more stringent Step Two diet is initiated (14).

Safety and efficacy of dietary therapy in infants, children, and adolescents

A low-fat diet is efficacious and safe in youth across the age spectrum, *e.g.* from the age of 7 months to the age of 7 yr and from 7–11 yr in STRIP (77–79) and from the ages of 8–10 yr throughout adolescence in the Dietary Intervention Study in Children (DISC) (80–82). In some studies, there were lower intakes of calcium, zinc, vitamin E, and phosphorus on low-fat diets. Therefore, although normal growth is achieved and maintained on low-fat diets, attention needs to be paid to ensure adequate intake of these key nutritional elements. Human milk remains the gold standard for infant feeding, and the higher TC in breastfed infants does not persist in childhood, adolescence, or adulthood (83).

The use of margarines (about three servings daily) high in either plant stanol esters (83, 84) or plant sterol esters (86) can reduce LDL-C an additional 10–15% when added to a low-fat diet. Water-soluble fibers (87) such as psyllium (88, 89) may also provide an additional 5–10% lowering of LDL-C.

Soy protein lowers VLDL-C and TG but not LDL-C and increases HDL-C (90, 91). Supplementation of a low-fat diet with an ω-3 fatty acid (docosahexaenoic acid 1.2 g/d) did not lower LDL-C but significantly increased the largest LDL subclass 91% and decreased the smallest LDL subclass 48% (92). Garlic does not lower LDL-C in hyperlipidemic children (93).

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

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 only been inferred from epidemiological studies (14). Insulin resistance is promoted in youth by obesity. A low saturated fat counseling program starting in infancy in STRIP improved insulin sensitivity in 9-yr-old healthy children (94), decreased obesity in girls (95), and enhanced endothelial function in 11-yr-old boys, but not in girls, effects mediated in part by the diet-induced reduction in TC (79).

Pharmacological therapy

Guidelines for the institution of drug therapy

The primary use of drugs in pediatrics is to lower significantly elevated LDL-C. Drug treatment to lower LDL-C is initiated at Tanner stage II in males and after menstruation in girls if the postdietary LDL-C is 1) more than 190 mg/dl and there is a negative or unobtainable family history of premature CVD or 2) more than 160 mg/dl and there is a family history of premature CVD or two or more risk factors for CVD or obesity or the metabolic syndrome is present (14, 58, 59).

The statins and the BAS are the two main classes of drugs currently used in children over 10 yr of age who have sufficiently elevated LDL-C (Fig. 1). Ezetimibe, a cholesterol absorption inhibitor (CAI) that blocks the absorption of cholesterol and plant sterols through the Niemann Pick C1 like 1 (NPC1L1) protein (Fig. 1), is also effective but is not yet approved by the Food and Drug Administration (FDA) for use in children, except in very rare cases of sitosterolemia (65) or homozygous FH (96). Each of these three agents reduce hepatic cholesterol, leading to release of the sterol regulatory element binding protein (SREBP) from the cytoplasm into the nucleus, where SREBP binds to the SRE of the promoter of the LDLR gene, increases the number of LDLR, and decreases LDL-C (97). Because SREBP also up-regulates the gene for hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase (97), the BAS and CAI are both associated with a compensatory increase in cholesterol biosynthesis, limiting their efficacy (Fig. 1). Therefore, BAS and CAI can be effectively used with the statins, which reduce hepatic cholesterol by inhibiting HMG-CoA reductase and decreasing cholesterol biosynthesis.

Niacin is not routinely used in pediatrics, although some FH homozygotes respond well to niacin (55–87 mg/kg·d in divided doses), due to the significant reduction of VLDL and LDL production (Fig. 1). Niacin might also be considered in children with strokes who have elevated lipoprotein(a) (98). Because aspirin is not used in children because of Reye's syndrome, ibuprofen can be used if necessary to prevent flushing. Use of a fibrate (48, 96, or 145 mg/d) is limited to that adolescent with TG over 500 mg/dl, who may be at increased risk of pancreatitis. Fish oils (1–2 g/d) lower TG by decreasing TG biosynthesis (Fig. 1), but the prescription version of ω-3 fatty acids is not yet approved by the FDA for use in children.

BAS

BAS were the only class of drugs recommended by NCEP for pharmacological lipid-lowering therapy because of their long track record of safety over three decades (14). In fact, the sequestrants have never been approved by the FDA for use in children. These agents suffer from significant tolerability issues as well as providing only a modest LDL-C reduction of about 15% (99–101). Liacouras *et al.* (101) found that 82.5% of children discontinued BAS after an average of 21.9 months, secondary to gritty taste and gastrointestinal complaints. The second-generation sequestrant, colesevelam (625-mg tablets, three or six per day), has a greater affinity for bile salts and can be used in a lower dose. Colesevalam is associated with less annoying side effects than cholestyramine, such as constipation and gritty taste, and does not interfere with the absorption of other drugs.

In randomized clinical trials, cholestryramine did not affect height velocity (100, 101). Levels of fat-soluble vitamins were maintained, except the BAS group had significantly lower 25-hydroxyvitamin D than the placebo group. Low folate and high homocysteine levels have been reported on BAS (99–101).

HMG-CoA reductase inhibitors

A number of randomized controlled trials (102–109) and a metaanalysis (110) showed high efficacy for LDL-C and apoB lowering and no increase in side effects, compared with placebo. Atorvastatin, lovastatin, pravastatin, and simvastatin are ap-

proved by the FDA for use in adolescents with FH. Starting doses are as follows 10 mg/d for atorvastatin, 40 mg/d for lovastatin, 40 mg/d for pravastatin, and 20 mg/d for simvastatin. All except atorvastatin are available generically.

Wiegman *et al.* (108) found that a 24% reduction in LDL-C in FH heterozygotes 8–15 yr of age with pravastatin significantly decreased carotid IMT compared with placebo. Younger age at statin initiation was an independent predictor of effect of treatment on carotid IMT in this Dutch study (111). Early statin therapy also restored endothelial function in children with FH (112). Early intervention with statins appears likely to reduce future atherosclerosis and CVD in those with FH.

The statins may also be useful in adolescents with FCHL or the metabolic syndrome when the LDL-C is more than 160 mg/dl after diet and weight control and multiple risk factors or a family history of premature CVD are present. If the LDL-C is less than 160 mg/dl after hygienic measures, metformin has been used in several studies of obese adolescents with the metabolic syndrome and hyperinsulinemia (113, 114).

Side effects of the statins in children and adolescents: liver and muscle

In a metaanalysis, (110), the prevalence of elevated alanine amino transferase 3 times above the ULN in the statin group was 0.66% (three per 454). Instances of asymptomatic increases (>10-fold) in creatine kinase, although unusual, have been reported in adolescents receiving statin therapy (110). No cases of rhabdomyolysis have been reported (102–110). Such adolescents are monitored two to three times a year for elevated alanine amino transferase and creatine kinase.

Special issues in young females

Adult women with FH and CAD may be more responsive to LDL-C lowering than men and have an overall favorable safety profile (115). The statins are effective and safe in adolescent girls, with no significant adverse effect on growth and development or on adrenal and gonadal hormones (105, 108, 109).

Statins are contraindicated during pregnancy because of potential risk to a developing fetus. Birth control is mandatory for those who are sexually active. Because of this concern, the long-term commitment to therapy, and the fact that CAD often occurs after menopause, some believe that statins should not be used to treat adolescent FH females. Others recommend treatment of adolescent FH patients, especially those with a strong 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.

Treatment of dyslipidemia secondary to other diseases

Type I diabetes

Youth with type I diabetes are at high risk for CVD as adults and already have increased carotid IMT (116). After dietary therapy and the best achievable diabetic control, the American Diabetes Association strongly recommends the use of statins in those with LDL-C of more than 160 mg/dl (116).

Nephrotic syndrome

The dyslipidemia in children with the nephrotic syndrome can be marked with TC and TG that approach 300 mg/dl or higher (117). Those patients who are unresponsive to steroids and have a postdietary LDL-C of more than 160 mg/dl may be at an increased risk for CVD (117) and warrant treatment with a statin.

Polycystic ovarian syndrome (PCOS)

PCOS presents in adolescence with menstrual disorders, acne, and hirsutism (118, 119). Insulin resistance and dyslipidemia are often present. After diet and weight control, an estrogen/progesterone combination is often used (118). Metformin can be considered, especially in those who are obese. Increased carotid IMT is present in young adults with PCOS (118, 119), and treatment with a statin can be considered in those with LDL-C higher than 160 mg/dl.

Summary

A number of clinical, epidemiological, pathological, metabolic, genetic, and randomized clinical trials strongly indicate that the origins of atherosclerosis and CVD risk factors begin in childhood and that treatment should begin early in life. The identification of youth at risk for early atherosclerosis includes an integrated assessment of predisposing CVD risk factors. Optimal detection of dyslipidemia in youth includes both selective screening of those whose parent has premature CVD or dyslipidemia or who themselves have obesity, multiple CVD risk factors, diabetes, nephrotic syndrome, or PCOS and universal screening at the age of 10 yr. Initial treatment of dyslipidemia includes a diet reduced in total fat, saturated fat, cholesterol, and simple sugars and increased in complex carbohydrates and, when necessary, weight reduction and aerobic. Effective dietary adjuncts include plant sterol-enriched margarines and psyllium. The primary use of drugs in pediatrics is to lower significantly elevated LDL-C. Statins are the drugs of choice and FDA approved for use in adolescents with FH or marked FCHL. BAS and CAI may also be used when indicated. Future studies are needed to determine whether treatment of dyslipidemia early in life prevents CVD in adulthood.

Acknowledgments

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Disclosure Summary: P.O.K. has received research grants from Abbott Pharmaceuticals, Pfizer, and Schering/Plough and honoraria from Schering/Plough and is on the Speaker's Bureau for AstraZeneca, GlaxoSmithKline, Merck, Pfizer, and Schering/Plough.

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