Evaluation of Hypercholesterolemia in Childhood

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IMPORTANT POINTS

1. Screening and treatment for hypercholesterolemia usually is reserved for children more than 2 years of age.
2. Using family history to identify children who have high cholesterol levels will miss a large number of children who have hypercholesterolemia.
3. Low HDL-cholesterol is a risk factor for atherosclerosis.
4. Hypercholesterolemia may be due to other diseases, including nephrotic syndrome and hypothyroidism.
5. Children more than 2 years of age should receive no more than 30% of their calories from fat.

Introduction

Atherosclerosis is a major cause of morbidity and mortality in the United States. It also is responsible for a large proportion of "premature" deaths and disabilities in young adults. Multiple factors that predispose people to develop heart disease have been identified. Compelling evidence links heart disease to hypercholesterolemia, cigarette smoking, hypertension, and diabetes mellitus. Additional factors associated with an increased incidence of heart disease include a low high-density lipoprotein (HDL)-cholesterol level, a family history of premature heart disease, and low levels of physical activity. The predictive value of "risk factors" identified more recently, such as personality type, levels of apolipoproteins A1 and B and lipoprotein (a), and distribution of fat (eg, central versus peripheral obesity), are understood less well.

Atherosclerotic diseases such as myocardial infarction and cerebral hemorrhage must be viewed as endpoints of a more prolonged disease process. The majority of people who have atherosclerosis are asymptomatic and have no demonstrable heart disease. Furthermore, several studies have documented that the process of "hardening of the arteries" begins during childhood and adolescence. For these reasons, several groups, including the National Cholesterol Education Program (NCEP) and the American Heart Association, suggest that prevention of premature atherosclerosis should begin in childhood.

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Atherosclerosis Begins in Childhood

Numerous epidemiologic studies have described a high incidence of atherosclerotic heart disease in countries such as the US and Finland, in contrast to the rarity of heart disease in countries such as Japan and China. These differences in disease incidence have led investigators to suggest that environmental forces play a role in the etiology of atherosclerosis. Studies of immigrants who "acquired" the risk factors after moving to areas of high prevalence also suggests that environmental forces predispose individuals to heart disease.

Studies during the Korean War showed that although many young American soldiers had evidence of coronary atherosclerosis, such evidence was virtually nonexistent among Korean soldiers. The Bogalusa Heart Study Group demonstrated that, among adolescents who died of accidental causes, arterial fat deposition correlated with premorbid lipid values. Studies from the Pathobiological Determinants of Atherosclerosis in Youth research group have shown that the risk factors of age, smoking, and elevated lipid levels correlate with atherosclerotic lesions found in young men who died as a result of accidents. Because both the atherosclerotic process and lifelong habits that influence cardiac disease (such as smoking, diet, and activity levels) begin early in life, it is appropriate to initiate preventive measures against atherosclerosis during these formative years.

Cholesterol Metabolism

Plasma total cholesterol is the sum of several types of cholesterol, including low-density lipoprotein cholesterol (LDL-cholesterol), high-density lipoprotein cholesterol (HDL-cholesterol), and very low-density lipoprotein cholesterol (VLDL-cholesterol). In practice, VLDL-cholesterol usually is estimated by dividing the more easily obtainable triglyceride (TG) level by 5. These levels are related through the following equation: Total Cholesterol = LDL-Cholesterol + HDL-Cholesterol + (TG/5). This equation is valid if the triglyceride level is less than 400 mg/dL.

Plasma cholesterol levels affected by two major systems or pathways. The exogenous pathway encompasses the effect of dietary intake on plasma cholesterol levels. Dietary cholesterol is ingested and absorbed, thus affecting the plasma cholesterol directly. Other dietary variables such as the amount of total and saturated fat ingested also are important in determining plasma cholesterol levels. Recent evidence suggests that our view of dietary effects may indeed be oversimplified and that each individual type of fat may affect plasma cholesterol uniquely.

The endogenous pathway consists of the cells' own synthesis and regulation of cholesterol. These processes are under genetic control and influenced in part by plasma and intracellular cholesterol levels and dietary fats. Other important factors include obesity, thyroid metabolism, and insulin levels.

Our understanding of the metabolic basis for hypercholesterolemia has been revolutionized by the finding that one common type of familial hypercholesterolemia is due to a genetic mutation in the LDL-cholesterol receptor. Several forms of LDL-cholesterol defects lead to an inability of the cell to bind and process cholesterol. Approximately 1 in 200 to 1 in

500 people are heterozygous for this LDL-cholesterol receptor defect. They have approximately twice the normal blood cholesterol level and, ultimately, are at a very high risk for premature coronary heart disease.

Atherosclerosis develops when cholesterol levels in the blood exceed the ability of the body to clear cholesterol from the blood stream, thereby leading to deposition of fat in the vessel wall. The most dramatic example of the early onset of atherosclerosis is in children who have homozygous familial hypercholesterolemia. These children are born with virtually no LDL-cholesterol receptor function and may have blood cholesterol levels between 600 to 1200 mg/dL. Xanthomas may appear in the first year of life, and patients often develop symptomatic and even fatal coronary artery disease in childhood or adolescence. The exact mechanisms of other genetic types of lipid abnormalities that predispose to early atherosclerotic heart disease are not as well established; however, some are associated with a low HDL-cholesterol level, apolipoprotein abnormalities, or elevated triglyceride levels.

Cholesterol Levels in Childhood

In childhood, the average total cholesterol level is approximately 150 mg/dL; this remains fairly stable from 2 to 18 years of age. The 95th percentile for this age group is approximately 200 mg/dL. There are small variations between African-American and Caucasian children and between boys and girls. Normal values for total and LDL-cholesterol in children and adolescents are presented in Table 1. Children who have heterozygous LDL-cholesterol receptor deficiency typically have a total cholesterol greater than 240 mg/dL and frequently near 300 mg/dL, well above the 99th percentile for age. When interpreting cholesterol values, it is important to realize that truly "normal" cholesterol values are unknown. Current "normal" values are based on children in the US and are divided into percentiles. Percentiles in other countries or societies often are different from those in the US. Current "normal" values should be used as guidelines for acceptable and high levels of cholesterol in children.

Identification of Hyperlipidemia in Childhood

The NCEP provides specific recommendations for cholesterol testing of children. Children older than 2 years of age whose parents or grandparents have premature (≤55 years of age) coronary heart disease should be tested. Coronary heart disease includes documented myocardial infarction, angina pectoris, cerebrovascular disease, sudden cardiac death, or angiographic evidence of heart disease. In addition, if a parent has high blood cholesterol (>240 mg/dL), the children also should be screened. The physician also may choose to screen children who are at increased risk for other reasons, such as hypertension or obesity, or whose family history is not available. Following these guidelines for selective screening will identify 40% to 60% of children who have elevated cholesterol levels.

Various plans have been proposed to increase the sensitivity of the testing; however, universal screening is essentially the only way to identify all children who have hypercholesterolemia. The NCEP chose not to recommend universal screening because of cost, difficulty with providing universal screening, incidence of false-positive results, and concerns about "labeling" children. In addition, some children who are identified as having a high cholesterol level in childhood will not meet treatment guidelines as adults.

TABLE 1. National Cholesterol Education Program Classification of Total and LDL-Cholesterol Levels in Children and Adolescents

CATEGORY	TOTAL CHOLESTEROL (MG/DL)	LDL-CHOLESTEROL (MG/DL)
Acceptable	<170	<110
Borderline	170–199	110–129
High	≥200	≥130

Screening Guidelines

A careful history concerning premature heart disease in parents or grandparents as well as details concerning hyperlipidemia in all family members should be obtained. If the parents have not had their cholesterol levels measured, they should be encouraged to do so.

Children who have a family history of premature heart disease require a lipoprotein analysis because they may be at increased risk for a low HDL-cholesterol level. A total cholesterol level should be obtained for children whose parent(s) has elevated cholesterol. If the cholesterol level is high (>200 mg/dL), a lipoprotein analysis should be performed. If it is acceptable (<170 mg/dL), the test should be repeated in 5 years. If the cholesterol level is borderline, it should be repeated within 2 to 4 weeks; if the average is borderline or high, a lipoprotein analysis should be performed.

Therapeutic Approach

Once a child has been identified as having hypercholesterolemia, a blood test should be repeated while the child is in a fasting state. If the total cholesterol level is high, a lipid profile should be obtained to ascertain the major determinants of the hypercholesterolemia. This approach will identify the small group of patients whose hypercholesterolemia is secondary to hypertriglyceridemia, those who have combined hypercholesterolemia and hypertriglyceridemia, and those who have a low or elevated HDL-cholesterol level. There is substantial variability between laboratories and even day-to-day variation of cholesterol values in a single individual. Therefore, the child should be fasting, in his or her usual state of health, and have at least two cholesterol levels measured before it is decided that his or her level is elevated.

Information about the child's general health and possible secondary

causes of hyperlipidemia should be part of the evaluation for hyperlipidemia. Children should be screened for symptoms of endocrine disorders (eg, hypothyroidism, diabetes mellitus, Cushing syndrome) and renal disease. Children should be questioned about drug use (steroids, contraceptives, seizure medications, isotretinoin) and drug abuse (anabolic steroids and ethanol). Details of the current diet can be summarized by asking about intake of eggs, type and quantity of milk and other dairy products, type of meat (beef versus chicken), type of spread (butter versus margarine), and cooking oils employed.

Physical examination for evidence of lipid deposition (eg, corneal arcus; planar, tuberous, or tendinous xanthoma) should be performed. Xanthoma are identified by their characteristic yellow-orange color and soft, nonpainful texture. They commonly are seen on the elbows and knees and over tendons. General health parameters, such as appropriate growth, blood pressure, and evidence of heart disease, should be identified. Attention to pubertal status is important because some children may have a decrease in total cholesterol during puberty, and knowledge of pubertal status will be useful in evaluating response to therapy. It often is useful to examine the parents or other family members briefly for the presence of xanthoma or corneal arcus, which may identify families that have LDL-receptor deficiency.

Causes of secondary hypercholesterolemia (Table 2) often are detectable on the basis of history or physical examination. Evidence for secondary causes of hypercholesterolemia, such as a goiter, hepatomegaly, or signs of nephrosis, should be sought. In some children it is advisable to perform other screening tests to exclude the presence of renal, thyroid, and hepatic disease, which may be silent in children.

TABLE 2. Secondary Causes of Hypercholesterolemia

Endocrine Causes	
	Diabetes mellitus
	Hypothyroidism
Renal Causes	
	Nephrosis
	Renal failure
Drugs	
	Adrenal steroids
	Isotretinoin
	Thiazides
	Anticonvulsants
	Certain oral contraceptives
	Alcohol
Hepatic Causes	
	Obstructive liver disease
	Hepatitis
Storage Disease	
	Gaucher disease
	von Gierke disease
Other Causes	
	Acute intermittant porphyria
	Anorexia nervosa
	Systemic lupus erythematosus
	Obesity

Treatment Guidelines

For children who have hypercholesterolemia, treatment should be based on the average of at least two lipoprotein levels according to the following guidelines:

Acceptable LDL-cholesterol (<110 mg/dL): Repeat analysis in 5 years.

Borderline LDL-cholesterol (<110–129 mg/dL): Step 1 diet, risk factor advice, and re-evaluation in 1 year.

High LDL-cholesterol (>130 mg/dL): Evaluation for secondary causes of hyperlipidemia, institution of dietary therapy, and testing of family members.

The first goal of any dietary therapy in children is to provide adequate calories for growth and development. Dietary therapy is aimed at a general decrease in the amount of total and saturated fat in the diet. Calories are maintained by providing increased carbohydrates. Both Step 1 and Step 2 diets provide an average of no more than 30% of calories from fat. The step 2 diet provides less saturated fat (7% versus 10%) and limits cholesterol intake to less than 200 mg/day (Table 3). These diets approximate diets of children in Greece, Israel, and Italy and are not associated with known growth or developmental problems. A recent multicenter study (DISC) suggested that among children who had moderate hypercholesterolemia, a moderately low-fat and low-cholesterol diet was effective in lowering LDL-cholesterol levels and was associated with normal growth patterns. The diet appeared safe in that no differences in serum hemoglobin, ferritin, zinc, or albumin levels were seen between the treatment group and controls.

Problems have been reported in children who have had caloric restriction in an attempt to decrease fat intake. It is important to stress that in children, cholesterol-lowering diets must provide adequate calories while at the same time limiting dietary fat intake. The role of a nutritionist is important. Children and their families need instructions and concrete examples of how to translate "30% calories from fat" into real meals. Furthermore, as children grow, their tastes and behaviors change. A nutritionist who has an understanding of family dynamics, as well as of childhood developmental stages, is key to successful dietary intervention.

Drug therapy usually is reserved for children older than 10 years of age who have failed an adequate trial of dietary intervention over a 6- to 12-month period. The NCEP pediatric panel suggests considering drug treatment in children 10 years of age who have 1) LDL-cholesterol ≥190 mg/dL or 2) LDL-cholesterol ≥160 mg/dL and a family history of premature heart disease or the presence of multiple associated risk factors.

Current drugs used for the treatment of children are the bile acid sequestrants—cholestyramine and colestipol. These have the ability to decrease a cholesterol level between 10% and 25% and are not thought to be absorbed systemically. The roles of new therapies such as water-soluble fiber and soybean proteins are not yet established, but may offer new, nonpharmacologic approaches. Other medications such as nicotinic acid, HMG CoA-reductase inhibitors, probucol, or gemfibrozil are not recommended for routine use in children or adolescents.

The long-term efficacy of treating children to prevent the onset of pre-

TABLE 3. Step 1 and Step 2 Diets

NUTRIENT	STEP 1	STEP 2
Calories	Adequate to promote normal growth and development	Same
Total fat	≤30% of calories	Same
Saturated fat	<10% of calories	<7% of calories
Polyunsaturated fat	Up to 10% of calories	Same
Monounsaturated fat	Remaining fat calories	Same
Cholesterol	<300 mg/day	<200 mg/day
Carbohydrates	Approximately 55% of calories	Same
Protein	About 15% to 20% of calories	Same

mature heart disease in adult life has not been studied and in all likelihood never may be determined adequately. Therefore, at this time, decisions to treat children with diet or medications must be based on information available in adults. Physicians must reach an agreement with the family in terms of weighing relative risks and benefits of beginning dietary therapy (low-risk) or of adding medications (slightly more risk) versus the risk of premature heart disease. Often families that have an especially strong history of early heart disease (eg, occurring in relatives in their 20s or early 30s) are willing to accept the inconvenience and low risks associated with aggressive treatment of hypercholesterolemia. Families that have no history of heart disease or in which heart disease occurred later (eg, 40 to 50 years of age) often do not want to start drugs and postpone medication use until teenage years or later.

Multiple Risk Factors Associated with Atherosclerosis

It is unusual for atherosclerotic heart disease to be due to only one specific cause; the children mentioned previously who have homozygous hypercholesterolemia are a unique example. Treatment plans and evaluation of family history should take into account the multiple risk factors that often contribute to coronary heart disease. These factors appear to increase risk in an additive manner. For example, the risk for heart disease in a 40-year-old male who smokes two packs of cigarettes per day and has a total cholesterol level of 240 mg/dL is similar to the risk for a nonsmoking 40-year-old male who has a cholesterol level of 400 mg/dL. Risk factors may be divided conveniently into those beyond the patient's control and those that can be altered by changing diet, lifestyle, or medications. Immutable risk factors include advancing age, sex, and family history of premature heart disease. Factors that may be altered by diet or treatment include the amount of elevated LDL-cholesterol and of decreased HDL-cholesterol, hypertension, and diabetes mellitus. Factors over which the patient may have even more control include cigarette smoking, obesity, level of exercise, and diet. These other risk factors may require special expertise for treatment. For children who have hypercholesterolemia, the other potential risk factors should be evaluated and patients provided with or referred for appropriate counseling or treatment.

Summary

For many adults, the risk of atherosclerosis can be reduced by intervention and treatment of known risk factors. Direct proof that similar intervention will be effective in children is not available. However, evidence suggests that prevention beginning in childhood will lead to a decrease in incidence of heart disease later in life. The majority of families are eager to take steps to prevent heart disease in their children, especially if there is a family history of early heart disease. It is the role of the pediatrician to identify those children at risk for early heart disease and to initiate advice on reducing risk factors.

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