Implications of childhood hypercholesterolemia

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■ Several studies have documented that hypercholesterolemia is common in American children. Other studies have shown that elevated cholesterol levels in childhood remain elevated well into adult life. Autopsy studies of adolescents have also found a strong positive correlation between antemortem cholesterol levels and early atherosclerotic changes in their aortas and coronary arteries. Collectively, these studies provide strong and consistent evidence that atherosclerosis begins in childhood. The evidence is also overwhelming that lowering elevated low density lipoprotein cholesterol levels reduces the risk of heart attacks caused by coronary heart disease, at least among middle-aged men. As a result, routine cholesterol and coronary heart disease risk factor surveillance in childhood is both productive and appropriate. Premature coronary heart disease may be largely preventable and atherosclerosis, if not preventable, can be significantly delayed.

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CARDIOVASCULAR disease is the eventual cause of death for nearly half of the U. S. population. This fact remains despite a 40% decline during the past 30 years in the age-adjusted mortality rate from cardiovascular disease.[1,2] The decreasing coronary heart disease mortality can be attributed to several medical interventions: improved identification and treatment of hypertension, increased surveillance of heart disease risk factors, and advances in specialized coronary care units.[3] In addition, the American public has become increasingly aware of health and physical fitness, and millions of adults have stopped cigarette smoking.

Symptomatic heart disease still affects 5.4 million people in the United States, and 1.5 million will experience a myocardial infarction in the coming year.[4,5] According to the Framingham Heart Study, 20% of men and 6% of women have coronary heart disease by age 60.[6] In addition, 6.7% of men and women eventually have a cerebrovascular accident.

Atherosclerosis is associated with several risk factors. Those that are modifiable include cigarette smoking, hypertension, obesity, physical inactivity, hypercholesterolemia, and diabetes. Nonmodifiable risk factors include age, male sex, and a family history of premature atherosclerotic disease or known hyperlipidemia. Hypercholesterolemia is the most basic and fundamental of the recognized risk factors.[7]

The evidence to support the cholesterol hypothesis is compelling.[8] The incidence of coronary heart disease increases as low density lipoprotein (LDL) cholesterol levels increase.[9] An expanding body of evidence indicates that lowering LDL cholesterol levels in hypercholesterolemic adults will reduce the incidence of coronary heart disease.[9–14]

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TABLE 1
EXPECTED DISTRIBUTION OF SERUM LIPID LEVELS, NORMAL CHILDREN 3 TO 19 YEARS OLD

Lipid type	5th percentile (mg/dL)	Mean (mg/dL)	95th percentile (mg/dL)
TC	120	160	200
LDL-C	65	100	130
HDL-C	35	55	70
TG	35	75	110

TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides.

EARLY ONSET OF ATHEROSCLEROSIS

Keys showed in 1975 that increases in dietary fat and cholesterol are accompanied by increases in the frequency of coronary heart disease around the world.[15] Countries without significant hyperlipidemia have a low incidence of cardiovascular disease. Keys commented that the greatest likelihood of success in preventing coronary heart disease lay in the control of risk factors at early ages.

Thirty years ago, Holman[16] documented the existence of fatty streaks in the aortas of nearly all American children over 3 years of age who were studied. He urged that atherosclerosis be considered a pediatric nutritional problem. Stary[17] noted fatty streaks in the coronary arteries of half the children 10 to 14 years old at autopsy; one third had macrophage foam cells in the intima of their coronary arteries. Seventy-seven percent of soldiers in their early 20s who were killed in the Korean and Vietnam wars had significant coronary atherosclerosis, and 5% had advanced coronary artery disease.[18,19] With increasing age and risk factor acquisition, these fatty streaks become fibrous plaques, which become advanced lesions.[20] These studies provide strong and consistent evidence that atherosclerosis begins in childhood.

HYPERCHOLESTEROLEMIA IN CHILDHOOD

Hypercholesterolemia is common in childhood. The Lipid Research Clinics program surveyed the plasma lipid and lipoprotein levels of 60,502 adults and children in 10 North American locations to obtain reference values for the US population.[21,22] *Table 1* contains the expected distribution of serum lipid levels for US children 3 to 19 years of age, based on the Lipid Research Clinics[21,22] and Bogalusa Heart Study[23,24] data.

The Bogalusa Heart Study[23,24] is an ongoing epidemiologic review of cardiovascular disease risk factors among Louisiana youth from birth through age 26. This study has provided lipid and risk factor data from 10,000 healthy, young individuals. Autopsies of adolescents (mean age, 18 years) from Bogalusa who died from such causes as accidents, homicides, and suicides, show a strong positive correlation between antemortem blood pressure and cholesterol levels and postmortem fatty streaks in the aortas and coronary arteries.

Several lipid surveillance studies,[25,26] including one of 6,500 children in a private practice setting in Parma Heights, Ohio,[27] have found nearly twice the expected number of children to have serum cholesterol levels above the 95th percentile (200 mg/dL). Cholesterol levels may vary considerably in different parts of country, depending on regional variations in dietary preferences and habits.

Elevated cholesterol levels in children beyond 2 to 3 years of age tend to remain high in adult life. The Muscatine Study[28] tested 2,446 young people at ages 8 to 18 and again at ages 20 to 30 for cholesterol levels and other cardiac risk factors. Ten years later, 43% of those children with initial cholesterol levels above the 90th percentile were still above the 90th percentile; 62% were above the 75th percentile, and 81% were above the mean. The Bogalusa Heart Study reported similar findings: more than 70% of children with elevated cholesterol levels remained hypercholesterolemic 12 years later.[29]

Orchard and colleagues[30] studied 611 individuals found to be hypercholesterolemic at age 12. At 21 years of age, 70% of the 611 subjects were still in the top two quintiles for cholesterol concentration. The statistical likelihood of remaining in a particular quintile over time due to chance alone is 20%. These data provide convincing evidence that the major predictor of adult hypercholesterolemia is hypercholesterolemia in childhood.

GENETIC CAUSES OF HYPERCHOLESTEROLEMIA

Genetic make-up strongly influences how individuals interact with environmental risk factors in the evolution of atherosclerotic heart disease. An estimated 5% of American children have a genetic predisposition for hypercholesterolemia and are therefore at increased risk for premature coronary heart disease.[31] Fifty to eighty percent of individuals who have coronary heart disease before age 55 have hyperlipidemia.[32] Clearly, modifiable coronary heart disease risk factors play an important role in premature coronary heart disease. The relative importance of genetics and environmental factors in the cause of hypercholesterolemia remains controversial.[7,33–38]

Several genetic lipid disorders can surface during childhood. Among the most common are familial hypercholesterolemia, familial combined hyperlipidemia, and polygenic hypercholesterolemia.[32]

Familial hypercholesterolemia (FH) occurs in 0.2% to 0.5% of the population. The heterozygous offspring has half the normal number of LDL receptor sites on cell membranes.[39] The condition is an autosomal dominant disorder and affects 4% of those patients with a cholesterol level above the 95th percentile (200 mg/dL). Ninety percent of such individuals have a myocardial infarction by age 60, and most have tendon xanthomas, corneal arcus, or xanthelasmas. It is the most common monogenic disorder in our society that eventually produces morbidity and mortality. Serum cholesterol is often twice the normal value, and half of first-degree relatives may also have the disorder. Individuals who are homozygous for the FH gene have essentially no LDL receptors. Plasmapheresis and liver transplantation, along with dietary and drug therapy, are usually necessary to reduce their cholesterol levels.

Familial combined hyperlipidemia, another autosomal dominant disorder, affects 1% to 2% of the American population.[40] Approximately 20% express the disease in childhood.[41] The underlying abnormality is probably caused by overproduction of very low density lipoprotein/apolipoprotein B (VLDL/Apo B) particles by the liver.[42] A third of such patients have hypertriglyceridemia, a third have hypercholesterolemia, and a third have both. Hypertriglyceridemia seems to occur early in childhood, whereas hypercholesterolemia occurs later in life. Familial combined hyperlipidemia can be diagnosed when multiple lipoprotein phenotypes are found in a single family.

Polygenic hypercholesterolemia occurs in approximately 1% of the population. The disorder may represent one or possibly combinations of several genetic defects that adversely affect LDL cholesterol metabolism. There may be an acquired deficiency of LDL receptors, but if so, it is not as severe as the deficiency in familial hypercholesterolemia. Cholesterol elevations are more moderate, and the relationship of cholesterol values among various relatives is approximately half what would be expected from a purely genetic origin.[32] Such individuals may be more sensitive to environmental risk factors, such as increased dietary saturated fat and cholesterol,[34] smoking, and sedentary lifestyle.

A low level of high-density lipoprotein (HDL) cholesterol is a strong and independent risk factor for coronary heart disease. Isolated low level HDL cholesterol levels (<35 mg/dL) may occur in 3% of the general population.[32] Possible causes include environmental factors, such as smoking, excessive alcohol consumption, and obesity. Some individuals have low HDL cholesterol because they have an autosomal dominant disorder[43] with incomplete penetrance that interferes with Apo A-I and Apo A-II metabolism.

SCREENING FOR HYPERCHOLESTEROLEMIA

Routine screening of children has shown that from 8% to 10% have cholesterol levels that exceed the Lipid Research Clinics' 95th percentile of 200 mg/dL. Assuming that 5% of children are genetically predisposed to premature coronary heart disease,[31] and that many will not manifest hypercholesterolemia until adult life, then approximately half of childhood hypercholesterolemia is caused by environmental factors—primarily diet.[44,45]

A recent report of 500 hypercholesterolemic children (mean age, 8 years) revealed that 85% had a definable phenotypic lipid disorder.[46] Only 5% (25) were identified as being hypercholesterolemic because they had HDL cholesterol levels above the 95th percentile and therefore were not at risk of future coronary heart disease. Thirty-two percent (160) of them had a primary or secondary relative with a premature myocardial infarction. These data support universal cholesterol surveillance in childhood and lipid profiles for those with total cholesterol levels above 200 mg/dL.

Pediatric cardiologists are beginning to identify families who are at increased risk for premature coronary heart disease. A family at risk is one with any member who has high LDL cholesterol concentration, a low HDL cholesterol concentration, coronary heart disease before age 55, essential hypertension, or who is 30% above ideal weight, or who smokes cigarettes.[47]

The National Heart Lung and Blood Institute and the National Institutes of Health's Office of Medical Applications of Research, as a result of a consensus conference in 1984,[48] concluded that lowering high LDL cholesterol levels reduces the risk of heart attack from coronary heart disease. The National Cholesterol Education Program has published guidelines for the detection and treatment of hypercholesterolemia in adults.[49] Currently, a panel of experts of the National Cholesterol Education Program is considering similar guidelines for children. Their report is expected to be released later this year.

The American Heart Association's Committee on Atherosclerosis and Hypertension in Childhood recommends that all children gradually decrease their consumption of cholesterol and saturated fat and that risk-

factor surveillance and advice regarding prudent lifestyle choices be provided to all children.[45] The Committee on Nutrition of the American Academy of Pediatrics recommends dietary changes[50] but currently advocates cholesterol screening only for children from high-risk families[51] (those with known hyperlipidemia or premature coronary heart disease). The American Health Foundation recommends universal cholesterol surveillance after 2 years of age and dietary modification for the entire population to lower cholesterol consumption.[4]

TREATMENT ISSUES

Children older than 2 years would benefit from the American Heart Association's Step I Diet, in which less than 30% of calories come from fat and less than 10% of calories come from saturated fat. Cholesterol consumption is limited to 100 mg per 1,000 kilocalories (less than 300 mg/day), and total calories are adjusted to maintain ideal weight. Limiting dietary saturated fat and cholesterol should cause no harm because cholesterol can be synthesized by the liver and the only essential fatty acids are polyunsaturated.[8] Frequent coronary heart disease risk factor surveillance, routine blood pressure monitoring, and advice regarding prudent lifestyle choices, such as avoiding cigarettes, adopting weight control measures, and regular physical activity, should be routine preventive health care for all American children and their families.[52–54]

Drug therapy for childhood hypercholesterolemia is more controversial and has been predominated by the bile-acid binding resins, cholestyramine and colestipol. Their long-term safety is generally accepted.[55] Drug therapy alone can achieve mean reductions of 20% in LDL cholesterol levels.[56] Gastric distress and constipation are not common side effects in children, in contrast to adults. Serum fat-soluble vitamins and folic acid may be monitored during therapy with resins, although levels associated with deficiency have not been observed.[57] Compliance is difficult because the drugs are not palatable.

For children 10 years old or older with a family history of premature coronary artery disease and in whom monotherapy is inadequate, niacin may be given in combination with cholestyramine. Niacin reduces LDL cholesterol and triglycerides, increases HDL cholesterol, and is inexpensive. Niacin is potentially hazardous, however, because of stomach irritation, flushing of the skin and, most importantly, liver toxicity. Therefore, careful monitoring of liver function is imperative during niacin therapy so that the drug can be stopped at the first sign of toxicity. The adverse effects clear when the drug is stopped. Combination therapy with cholestyramine and niacin can reduce LDL cholesterol levels by approximately 35%.[56] Inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, such as lovastatin, should be prescribed cautiously in childhood because the long-term effects of drugs that inhibit metabolic pathways are unknown. More information and new medications are needed to make possibly lifetime pharmacotherapy reasonable for the at-risk pediatric population.

CONCLUSION

Dietary modification for the entire population after 2 years of age to reduce intake of cholesterol and saturated fat intake appears entirely appropriate. Universal cholesterol screening of all children after 2 years of age is supported by the studies reported in this review.[7,23,25,27,30,47] In general, children who have LDL levels greater than 160 mg/dL and at least two other risk factors, or LDL levels greater than 190 mg/dL with or without risk factors, may be candidates for more intensive dietary manipulation and possibly pharmacotherapy. These children also may need referral to pediatric hyperlipidemia clinics.

Children from high risk-families are in a special risk group; these children and should routinely have lipid profiles rather than simple cholesterol screening. When the family history shows premature coronary heart disease and a specific diagnosis is unclear, specialized studies may be appropriate, such as measurement of Lp(a),[58] HDL-2,[47] Apo A-I, and Apo B levels.[59,60]

Molecular biologists and geneticists will clarify many lipid disorders in the future. The US Preventive Services Task Force has stated that, "Abundant evidence documents that the majority of deaths among Americans under age 65 are preventable, many through interventions best provided in a clinician's office."[61] Premature coronary heart disease may be largely preventable. Atherosclerosis can be significantly delayed, if not prevented.

With respect to whether or not atherosclerosis begins in childhood, Milton's statement[62] may be remarkably prescient: "Childhood shows the man as morning shows the day."

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