

Hypercholesterolemia in Children

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During the last decade, major changes have occurred in the approach to the diagnosis and treatment of hypercholesterolemia in children. In 1993 the National Cholesterol Education Program Expert Panel on Blood Cholesterol in Children and Adolescents recommended that selective screening for the diagnosis of hypercholesterolemia be implemented, and that diagnosed children be treated based on their low density lipoprotein cholesterol levels and identified risk factors [1]. Following these recommendations, a plethora of studies examined the efficacy and safety of low fat diets in treating childhood hypercholesterolemia. In addition, drug therapy of childhood hypercholesterolemia was examined using approved and non-approved drugs. This review explores the rationale for the NCEP guidelines and current knowledge on dietary and drug treatment of pediatric hypercholesterolemia.

Rationale for cardiovascular disease preventive measures in childhood

Evidence that atherosclerosis begins early in life comes from both clinical evidence and epidemiological data. The strongest clinical data are provided by children with homozygous familial hypercholesterolemia. These children develop significant coronary heart disease in the first decade of life and frequently die from myocardial infarction before the age of 20 [2,3]. Furthermore, blood cholesterol levels measured at 22 years of age predict the risk for CHD over the next 30 to 40 years [4], and data from the Framingham Study show that cholesterol levels measured in young adult males and females predict CHD mortality 30 years later [5]. In familial hypercholesterolemia there is a direct association between the duration and severity of the hypercholesterolemia and extravascular lipid deposition in tissues of these patients [6].

Epidemiological data support the relationship between childhood cholesterol levels and adult levels [7,8] and the relationship between hyperlipidemia in childhood and parental premature CHD [9,10]. Pathological findings provide further evidence about the early development of atherosclerosis; for example a high frequency of advanced

coronary artery lesions was found in young soldiers killed in the Korean War [11]. In addition, a quantitative post-mortem estimation of atherosclerosis in coronary arteries and aortas of children and young adults demonstrated a significant relationship between hyperlipidemia and the extent of atherosclerosis [12]. In agreement with the accumulating evidence, it has been shown that cardiovascular risk factors found in children are related to the severity of atherosclerosis found postmortem in these individuals dying as young adults [13]. Thus, identifying risk factors for CHD in children may predict the likelihood of developing CHD as adults, providing the strongest argument for identifying and treating these risk factors.

Studies in adults provide unequivocal evidence that reduction of serum cholesterol concentrations lowers the risk of CHD [14]. The effectiveness of diet in reducing total and LDL-cholesterol levels is well established and has significant beneficial effects on cardiovascular risk factors [15]. Furthermore, studies in young children and adolescents have shown that when adequate calories and nutrients are provided, cholesterol-lowering diets are effective in reducing LDL-cholesterol levels without impairing growth and development [16-19].

Screening for childhood hypercholesterolemia

Cholesterol screening in childhood is controversial. It has been suggested that childhood screening not be performed because the outcome of treating children with hyperlipidemia is unknown [20], that cholesterol measurements performed outside of research centers may be inaccurate [20], and that some children with elevated plasma cholesterol levels do not continue to have increased levels as adults [8]. However, several studies have demonstrated that childhood rank order of cholesterol is maintained over time [7,21], and that when cholesterol levels in children were higher than the 90th percentile on two occasions 75% of the children had high cholesterol levels as adults [8]. Furthermore, in a study examining adults who had been examined as children, it was found that reduced cholesterol levels as adults was partially due to adopting

NCEP = National Cholesterol Education Program Expert Panel on Blood Cholesterol in Children and Adolescents
CHD = coronary heart disease

LDL = low density lipoprotein

changes of lifestyle in childhood that resulted in modification of risk factors [21]. In addition, diagnosis of hypercholesterolemia in a child can identify parents at risk for premature heart disease [22,23].

In the United States, current pediatric recommendations regarding cholesterol screening are to selectively screen children above the age of 2 with a positive family history of hypercholesterolemia and/or early heart disease (i.e., a pool of patients enriched in genetic factors predisposing to heart disease) and those children in whom a family history cannot be obtained (i.e., adopted children) [1]. A positive family history of premature CHD is defined as a parent, grandparent, or first-degree aunt or uncle who experienced one of the following before the age of 55: myocardial infarction, angina pectoris, peripheral vascular disease, cerebrovascular disease, sudden cardiac death, or documented coronary atherosclerosis. Parental hypercholesterolemia is defined as total blood cholesterol of 240 mg/dl or higher. The presence of other conditions commonly associated with increased risk of coronary heart disease, such as smoking, diabetes, obesity and hypertension, are also reasons for checking cholesterol levels.

Initial evaluation and follow-up of children with hypercholesterolemia

For children with a positive family history of premature CHD, fasting lipoprotein analysis (total cholesterol, total triglycerides, high density lipoprotein cholesterol and LDL cholesterol) should be performed. For children, fasting means consuming nothing except water after midnight. Lipoprotein profiles should be performed twice and an average of the two determinations should be used for further evaluation and treatment. In the absence of a familial history of premature CHD, but with parental hypercholesterolemia or other risk factors, a non-fasting TC is sufficient as the initial test. Levels of total cholesterol and the various lipoproteins are different in children and adolescents compared to adults [20]. Total cholesterol in the umbilical cord blood is approximately 70 mg/dl, and the 50th percentile after 2 years of age is 162 mg/dl. Acceptable TC levels are lower than 170 mg/dl [Table 1]. If the TC level is elevated, the above-described fasting lipoprotein analysis should be performed to confirm the first result, as well as to determine the LDL-C level. Table 1 provides acceptable, borderline and high LDL-C levels.

For any child with high cholesterol (either TC or LDL-C), screening tests for secondary causes of hypercholesterolemia (in particular, diabetes and diseases of the thyroid, liver and kidney) should be obtained. Certain medications (such as steroids, anti-convulsants and oral contraceptives) can also be secondary causes. A list of secondary causes of hypercholesterolemia is given in Table 2.

TC = total cholesterol

Table 1. Cutoff points of total and LDL cholesterol for dietary intervention in children and adolescents with a family history of premature cardiovascular disease or hypercholesterolemia

| Category | Total cholesterol (mg/dl) | LDL cholesterol (mg/dl) |
|------------|---------------------------|-------------------------|
| Acceptable | <170 | <110 |
| Borderline | 170–199 | 110–129 |
| High | >200 | >130 |

Table 2. Secondary causes of hypercholesterolemia

| |
|---|
| Endocrine |
| Hypothyroidism |
| Hypopituitarism |
| Diabetes mellitus |
| Metabolic |
| Gaucher disease |
| Glycogen storage disease |
| Tay-Sachs disease |
| Niemann-Pick disease |
| Renal |
| Nephrotic syndrome |
| Hemolytic uremic syndrome |
| Liver disease |
| Hepatitis |
| Cholestasis (benign recurrent intrahepatic cholestasis, congenital biliary atresia, allaglyle syndrome) |
| Medications |
| Androgens |
| Diuretics (thiazide diuretics, loop diuretics) |
| Glucocorticoids |
| Immunosuppressive agents (cyclosporine, tacrolimus) |
| Oral contraceptives |
| Retinoids |
| Miscellaneous |
| Anorexia nervosa |
| Systemic lupus erythematosus |
| Klinefelter syndrome |
| Idiopathic hypercalcemia |

Management of childhood hypercholesterolemia

The goal of dietary treatment is to reduce LDL-C levels. Table 1 provides the cutoff points of total and LDL-cholesterol for dietary intervention in children and adolescents with a family history of hypercholesterolemia or premature CHD. The recommended initial management to achieve this goal in children is to institute a "heart-healthy diet," i.e., one that is low in cholesterol and saturated fat, high in complex carbohydrates, and adequate in energy for growth and the maintenance of a desirable weight. The American Heart Association Step I diet is well established for this purpose in adults and in children over age 2 [24]. In a Step I diet, no more than 30% of total calories are from fat, less than 10% of total calories are from saturated fat, and cholesterol is restricted to 100 mg/1,000 kcal, not to exceed 300 mg/day. Many foods high in cholesterol are also high in saturated fat. A Step I diet substitutes foods rich in monounsaturated and polyunsaturated fats for those rich in saturated fats. The Step I diet does not mention trans-unsaturated fatty acids, the product of commercial hydrogenation of vegetable oils. In 1995, a consensus panel concluded that there is insuffi-

cient evidence to recommend reduction in trans-fatty acids consumption [25]. However, these fatty acids increase LDL-C serum levels and decrease serum HDL-C serum levels (saturated fats increase both LDL-C and HDL-C serum levels), and it is reasonable to suggest that their consumption be limited too [26,27]. A complete dietary assessment is required to comprehensively estimate the intake of energy and of major and minor nutrients.

Table 3 provides the target goal for each LDL-C level category after dietary intervention. Although the goal is to lower LDL-C to less than 110 mg/dl, in some cases this will not be possible. There are multiple reasons for the failure of dietary intervention: the child may already consume a reasonably heart-healthy diet, the elevation may be high enough so that the percent reduction achieved by dietary modification (typically no more than 20% and frequently less than 10%) still may not lower LDL-C to the target goal, and that children with inherited hypercholesterolemia tend to have a lower response to dietary modification [28]. Therefore, a more realistic goal for children and adolescents with high LDL-C is to reduce the level to lower than 130 mg/day, which is given in Table 3 as the minimal goal.

To confirm the effectiveness of dietary changes, LDL-C should be checked 3 to 6 months after treatment is started and yearly thereafter. Because lowering LDL-C levels reduces the progression of CHD, the importance of any lowering of LDL-C levels cannot be overemphasized. Nonetheless, if the Step I diet does not achieve even the minimal goal, then the NCEP recommended dietary approach is to try a more restrictive diet (Step II), which contains less than 7% of total calories from saturated fat and cholesterol less than 75 mg/1,000 kcal. Despite the seemingly modest changes relative to the Step I diet, with this diet the potential exists to develop nutritional deficiencies (due to the more limited food selection); thus patients placed on the Step II diet must be closely monitored by someone with considerable nutritional expertise.

When carefully executed, dietary management in children is safe and successful [16–19]. Even a minor modification may be successful, as demonstrated in a study where isocaloric substitution of whole milk with low fat milk containing oleic acid achieved a 7% decrease in TC, a 9% decrease in LDL-C, and a 13% decrease in triglycerides in children aged 3–9 years old [29]. In addition, it

has been shown that soluble fiber like psyllium has a cholesterol-lowering effect in children [30], including an additional cholesterol-lowering effect to that observed with the Step I diet in children in one study [31] but not in another [32]. Another approach is the use of plant sterol esters that reduce cholesterol absorption, increase cholesterol elimination in feces as cholesterol and not as bile acids, and increase cholesterol synthesis. Plant stanol ester margarine reduces LDL-C in adults and children with familial hypercholesterolemia with additive response to drug therapy. The stanol esters have a milder though still significant effect on healthy children already consuming a low fat diet, but this is accompanied by reduced serum beta-carotene to LDL-C ratio [33].

Other risk factors for CHD, such as cigarette smoking, physical inactivity and obesity tend to develop during childhood and adolescence. Recommendations should be made for appropriate lifestyle modifications, such as maintaining a desirable weight, increasing exercise, reducing sedentary activities (e.g., television watching), and quitting smoking. Treatment programs begun in childhood improve the long-term lifestyle adherence and may reduce the risk factors in these families [20]. Involving all family members in the dietary changes and lifestyle modifications is important for long-term adherence to these treatment modalities.

Medications in childhood hypercholesterolemia

The NCEP has recommended that drug therapy be considered for children above the age of 10 who have had an adequate trial of dietary treatment for 6–12 months with LDL-C levels remaining above the 99th percentile (LDL-C >190 mg/dl) [1]. In addition, drug therapy should be considered when LDL-C levels remain above the 95th percentile (LDL-C >160 mg/dl) and there is a positive family history of premature CHD or the child has two or more CHD risk factors. These risk factors include cigarette smoking, elevated blood pressure, low HDL-C (<35 mg/dl), severe obesity (>30% overweight), diabetes mellitus and physical inactivity.

The only class of drugs that have been recommended for children and adolescents are the bile salt sequestrants (cholestyramine). These bile acid-binding resins bind bile salts and increase their fecal excretion. The decreased intestinal bile salts decrease cholesterol absorption. In addition, there is increased hepatic LDL receptor activity (resulting in lower LDL-C blood levels) due to the increased hepatic needs for cholesterol to replace the bile salts lost from the enterohepatic circulation. These drugs are not absorbed by the intestine, they lack systemic toxicity, and their usage is considered safe for children and adolescents. A packet of cholestyramine contains 4 grams of the resin. It is recommended that cholestyramine be started at 2 g twice a day with the two major meals for maximum effect [20]. The NCEP and

Table 3. Goals of diet therapy

| Category | LDL-cholesterol | |
|------------|--------------------------|-----------------------------|
| | Initiation level (mg/dl) | Goal (mg/dl) |
| Borderline | 110–129 | <110 |
| High | >130 | < 130 minimal <110 ideal |

HDL-C = high density lipoprotein cholesterol

others have suggested that the maximal dose of cholestyramine is 16 g/day [1,20]. However, doses up to 8 g of cholestyramine per day provide the greatest cholesterol reduction [34], and larger doses increase the prevalence of side effects without a further significant reduction in LDL-C blood levels [34]. In children, cholestyramine reduces LDL-C cholesterol levels by more than 15% [35,36], but compliance appears to be a major problem. Despite the lack of systemic effects, more than 50% of children discontinue the medication after less than one year because of nausea, epigastric fullness, bloating, flatulence, and constipation [35]. Our experience in Israel demonstrated that about 60% of the children stop taking the medication within 24 months (unpublished data), usually because of a bad taste, which concurs with the findings of others. Mixing the resin with cold juice, the use of a straw, and taking the resin at the end of the meal may improve compliance. Since fat-soluble vitamins and folic acid absorption may be impaired, their supplementation is recommended. Other medications should be taken 1 hour before or 4 hours after the resin, and it should be kept in mind that obese children and children with familial combined hyperlipidemia may respond with a significant elevation of blood triglyceride levels [35].

The goal of drug therapy is similar to the dietary goals [Table 3], namely to achieve normal LDL-C levels. However, it is important to emphasize that the percent reduction in LDL-C is more important than the absolute blood level achieved [34] and that normal blood levels cannot be expected in children with LDL-C in the drug therapy recommended range.

Other than cholestyramine, all drugs are absorbed and have systemic effects. Nicotinic acid has been used successfully alone or in combination for the treatment of childhood hypercholesterolemia [20,34]. However, nicotinic acid causes side effects in a significant percentage of children (especially flushing and liver enzyme abnormalities). When drug therapy other than cholestyramine is considered, the next step often considered is the use of HMG-CoA inhibitors (statins). These drugs inhibit the major step in cholesterol synthesis and cause a significant reduction in LDL-C, a modest decrease in blood triglyceride levels, and slightly increased blood levels of HDL-C. In adults, these drugs have proved successful in both secondary and primary prevention of CHD [37]. In children, short-term treatment with various statins reduce LDL-C blood by an average of 25% [38–40]. The treatment is safe; elevations of liver enzyme levels and creatine kinase are uncommon [38,39]; and growth, hormonal and nutritional status are not impaired during adolescence [38]. The role of statins in adolescent females (after menarche) is currently being investigated in a multicenter prospective trial, and studies looking at newer more potent statins are in preparation.

Due to the lack of data on the long-term safety and efficacy of these drugs, it is our practice to offer statin treat-

ment only to children with LDL-C levels above 250 mg/dl, or to those children whose parent died before his or her 40th birthday due to premature CHD.

In summary, since atherosclerosis begins in childhood, there is a rationale for screening children and adolescents at high risk of developing CHD. Treatment of hypercholesterolemia during childhood and adolescence is based on dietary treatment and lifestyle modification. Drug therapy should be limited to children with levels above the 99th percentile who fail to reduce their levels after 6–12 months, and successful treatment is considered to be any reduction of LDL-C cholesterol accompanied by changes to an appropriate lifestyle and healthy eating habits.

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