# Pediatric hyperlipidemia: the Cleveland Clinic experience 1979–1981

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In the United States, a middle-aged male Caucasian now has a one in five chance of developing clinical coronary heart disease before his 60th birthday,[1] and a one in three chance of dying during the initial coronary attack. This is one of the highest incidences in the world.

Coronary disease may actually begin very early in life. Fatty streaks are commonly found in the intima of children the world over, even in countries with a low incidence of coronary artery disease. Progression from fatty streak to fibrous plaque has not been convincingly documented, but cross-sectional studies suggest that some fatty streaks do progress to fibrous plaques and that these changes occur in the same vessels.[2] This progression suggests that atherosclerosis is a pediatric problem.

Many environmental as well as genetic factors play a role in the development of atherosclerotic lesions. Genetic predisposition to coronary heart disease, hyperlipidemia, hypertension, and smoking are the major primary risk factors.[1] Secondary factors are sedentary living habits, obesity, psychosocial tension, diabetes mellitus, gout, and long-term maintenance hemodialysis for renal failure. Atherosclerotic lesions seem to be related to serum cholesterol and dietary fat when comparing populations, but this association cannot be confirmed on

an individual basis.[3] Since the extent of coronary atherosclerosis varies among individuals of similar race, sex, geographic location, disease, and smoking habits, other important factors must be involved.

However, if the occlusive complications leading to clinical disease can be prevented, it seems reasonable to initiate programs of prevention as early as the first decade. In 1979, we established a clinic to evaluate hyperlipidemia in children at the Cleveland Clinic Foundation. This report details our initial experience with the patients referred to the Pediatric Hyperlipidemia Clinic from 1979 to 1981.

## Materials and methods

From 1979 to 1981, 67 patients were referred to the Pediatric Hyperlipidemia Clinic ranging in age from 18 months to 20 years (mean, 11 years). All patients had complete histories, physical examinations, and laboratory studies to rule out secondary causes of hyperlipidemia.

The lipid abnormalities seen in the 67 patients are listed in the *Table*. Evaluations in 27 of the 67 patients (40%) revealed normal lipid levels. Most of these patients had been referred from an outside physician who had determined on only one evaluation that the cholesterol was slightly high for age; on repeated testing in our clinic, however, lipid levels were within normal range.

Thirteen patients (19%) had elevated total serum cholesterol, predominantly in the low-density lipoprotein fraction (LDL) characterized as a Type II hyperlipidemia by the Frederickson classification.[4]

In 12 patients (18%) elevations were predominantly in triglycerides (Type IV). In 12 others (18%) only the HDL fraction was elevated, with normal LDL and triglyceride levels. Two patients (3%) had hyperlipidemia of the mixed type.

**Table .** Cleveland Clinic Hyperlipidemia Clinic, 1979–1981

| | |
|---|---|
| Normal* | 27 |
| Increased LDL-C (Type 2) | 13 |
| Increased triglycerides (Type 4) | 13 |
| Increased HDL-C only | 12 |
| Mixed type | 2 |
| Total patients | 67 |

* Normal = <200 mg/dl for cholesterol and <150 mg/dl for triglycerides.

All patients underwent at least three 9- to 14-hour fasting total cholesterol, triglyceride, HDL cholesterol, and lipoprotein electrophoresis evaluations. Only after a consistent pattern was established by these three measurements were dietary and exercise recommendations made.

## Dietary instruction

The objective of nutritional counseling was to implement modified fat diets for children or adolescents identified as having some lipid abnormality. The process was threefold: interviewing, counseling, and consulting to help parents and children acquire more healthful dietary habits. A detailed nutrition profile and family history were obtained. Patients whose weight was greater than 10% above the ideal were measured with Lange's skin-fold calipers. Overweight was taken as the difference between actual and ideal weight. Height, sex, and body build were also taken into consideration.

Dietary history was evaluated for energy and nutrient adequacy. The patient and parents were given detailed dietary instruction materials with sample menus. The diet provided adequate protein and calories for optimal growth and development yet limited cholesterol and saturated fats to 300 mg, decreased

sugar from 18% to 10% and salt from 10 to 5 g/day, and increased fruits, vegetables, total fiber, and polyunsaturates to 20% of total calories. Diet records were evaluated every two weeks to assess compliance. The patients were given positive reinforcement via telephone or written communication.

In patients with Type II hyperlipidemia, foods rich in saturated fats such as meat, milk, and butter were restricted. Beef, pork, and lamb were limited to 3 oz three times a week, milk fat was decreased to 10% or less depending on the age of the patient, and soft margarines with vegetable oils and high cholesterol foods such as egg yolks, liver, brain, and kidneys were forbidden.

Patients with hypertriglyceridemia were given a low-sugar diet, and advised to reduce to their ideal body weight. None of the patients was initially given medication

In patients with Type IV hyperlipidemia, the instructions included sucrose (simple sugars) restriction, weight reduction, and an increase in physical exercise. In all of the children with hyperlipidemia, special emphasis was placed on eating fish, poultry, veal, and lean meats.

### Exercise recommendations

All patients were initially given a regular daily exercise program. This included jumping rope for 10 minutes each day, increasing by 10- to 15-minute increments over a two- to three-week period. Other patients were instructed to run or swim for the same amount of time, and to increase their exercise time

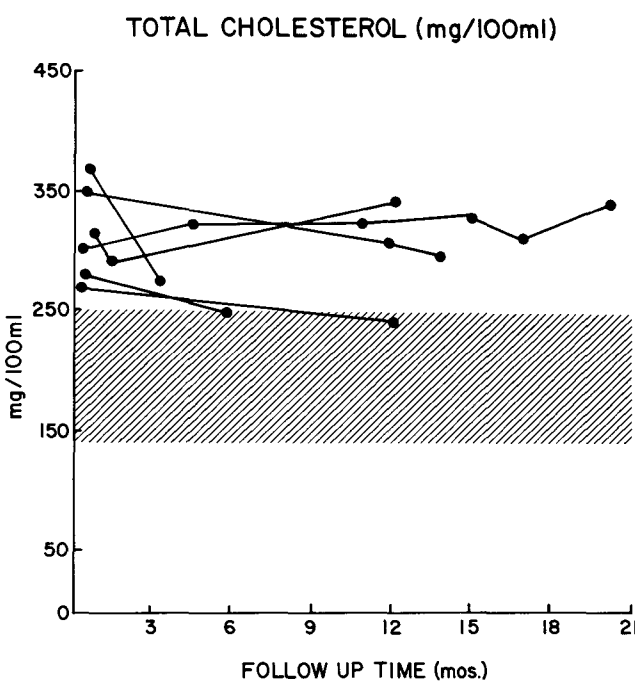


**Fig. 1.** Total cholesterol levels measured in 6 patients with Type II hypercholesterolemia followed for a mean time of one year. Note that serum cholesterol levels were elevated in all patients above the 95th percentile. Normal ranges are listed in the hatched boxes taken from data from the Rochester, Minnesota study.[20]

by 10-minute increments at intervals of two to three weeks.

## Results

Six patients with hypercholesterolemia with elevations of LDL were followed from two months to two years, with a mean follow-up of one year. *Figure 1* lists the initial total cholesterol and subsequent determinations following dietary and exercise intervention. All patients initially had elevated total serum cholesterol concentrations above the 95th percentile for age, and in general, there was a trend to a lowering of cholesterol with dietary and exercise intervention. In most cases, however, the total serum cholesterol remained elevated as did the LDL cholesterol. Only two patients whose cholesterol levels were mildly elevated had the normal range for age at follow-up.

*Figure 2* shows the results of dietary and exercise intervention in 7 patients with hypertriglyceridemia followed four months to two years, with a mean follow-up of one year. Triglyceride levels returned to normal ranges in all but 2 of these patients, even in those with triglyceride levels above 500. For example, one patient's triglyceride level fell from approximately 580 to 190 mg/dl. Another's triglycerides (the most elevated in our group) fell from more than 2000 mg/dl to below 500 mg/dl with diet and exercise. However, the patient

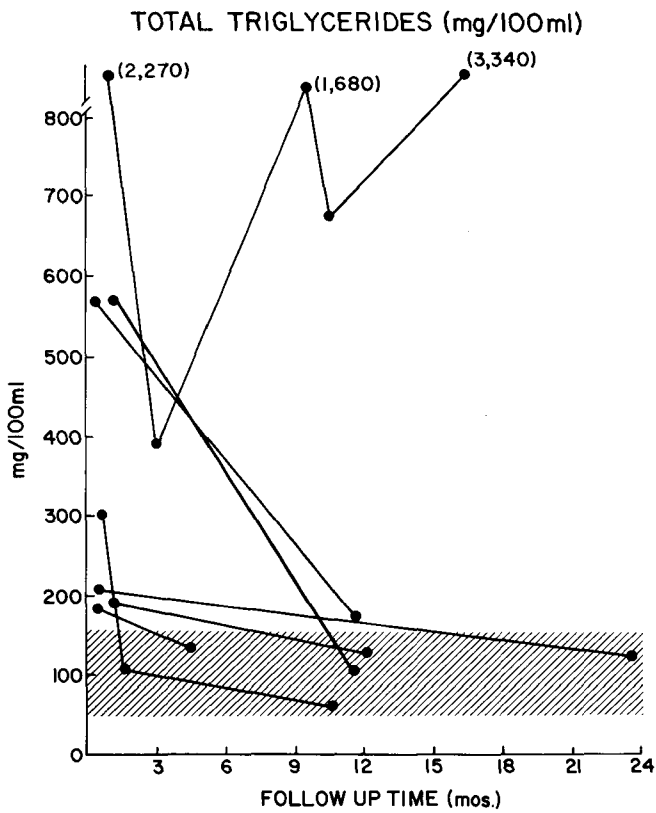


**Fig. 2.** Total triglyceride levels measured in patients followed for a mean time of one year. Levels returned to normal in almost all patients despite markedly elevated triglyceride levels before therapy.

later ignored the dietary and exercise instructions and the triglycerides returned to a markedly elevated state.

The HDL cholesterol levels in patients with hypertriglyceridemia are shown in *Figure 3*. Note that the HDL levels are in the low normal range. Conversely, in patients with elevated HDL levels, the triglycerides fall in the low or low normal range (*Fig. 4*).

## Discussion

Our 1979 lipids surveillance in young people was based on the following premises:

1. *Elevated serum cholesterol increases the risk of premature coronary disease.* The International Atherosclerosis Project (IAP), an extensive study of the geographic pathology of atherosclerosis,[5] correlated the relationships of various risk factors for coronary artery disease with the atherosclerotic lesions themselves. The rank correlation of lesions with serum cholesterol is 0.75, which is significantly greater than 0 ($p > .001$). No one has conclusively shown that elevated serum triglycerides pose an increased risk factor for early atherosclerotic disease.

2. *If the atherosclerotic process is identified early, and preventive measures, particularly diet, exercise, and medication are begun immediately, they can effectively implement primary prevention.* The Helsinki Medical Hospital Study in adults demonstrated a 50% reduction in deaths from coronary artery disease over a two- to six-year period and a 12%–18% decrease in cholesterol in hospitals serving foods high in polyunsaturated fat.[6] In a more recent study[7] of 1232 men, a subgroup was instructed to lower their blood lipids by a change of diet and to stop smoking.

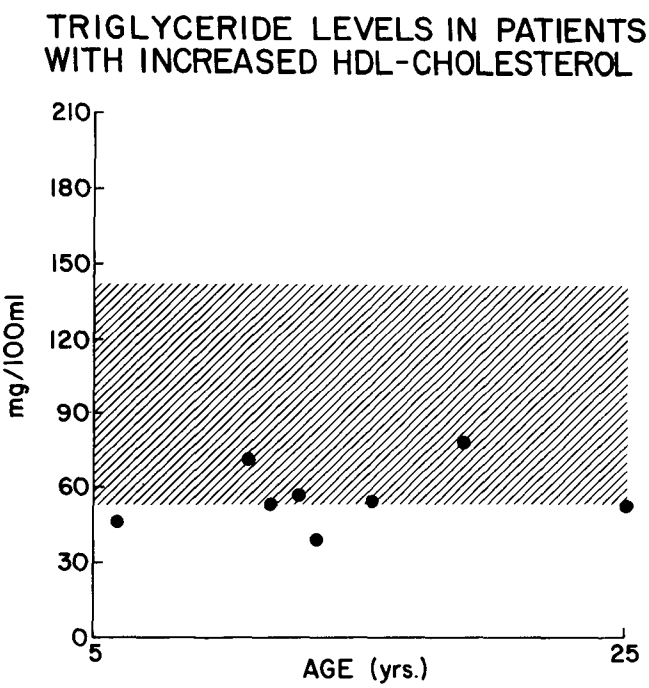


**Fig. 3.** Triglyceride levels in patients with elevated HDL cholesterol demonstrating normal to low normal, or abnormally low triglyceride levels.

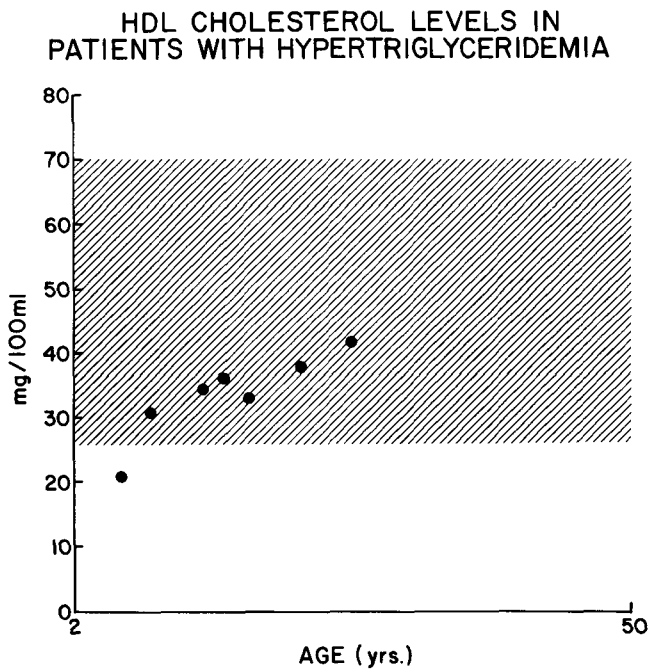


**Fig. 4.** HDL cholesterol levels in patients with hypertriglyceridemia related to age. The cross-hatched areas represent the normal range established in the Rochester, Minnesota study.[20] HDL cholesterols tend to be in the low normal range.

Mean serum cholesterol concentrations were approximately 13% lower in the intervention group than in the control group, mean fasting serum triglycerides fell by 20%, and the mean tobacco consumption per man decreased by more than 45%. Diagnosis of cardiovascular disease during the study was made blindly. At the end of the observation period, the incidence of myocardial infarction (fatal and nonfatal) and sudden death was 47% lower in the intervention group than in controls.

In 10% to 20% of children heterozygous for familial hyperlipidemia (ages 7–21), outpatient diet alone may reduce total and LDL cholesterols to normal. In our study and in that of Glueck et al,[8, 9] however, intensive diet and exercise lowered the total serum cholesterol level, but it rarely returned to normal range for age. In addition, the routine use of resin therapy, such as cholestyramine (Questran) and cholestipol (Cholestid), has resulted in further reductions of cholesterol of only 20%–30%.[10] However, combining cholestyramine or cholestipol with clofibrate (Atromid-S) not only reduces cholesterol 20%–30%, but may also change its composition. In combining the two therapies, clofibrate may effect an increase in HDL cholesterol levels and a decrease in LDL levels.[11]

In another combined drug study, Kane et al[12] used colestipol combined with niacin and achieved a total serum cholesterol decrease of 45%. The LDL levels decreased 55%, whereas HDL levels increased. Side effects were infrequent although nicotinic acid has been shown to cause gastric irritation, pruritis, flushing, and skin changes in children. In our patients with hypercholes-

terolemia, there was a definite trend toward a reduction of cholesterol with diet and exercise, but most of them should begin additional drug therapy to see if these cholesterol levels can be reduced to the normal range.

An interesting finding was that 18% of our patients with elevated total serum cholesterol had elevations only in HDL cholesterol. This compares to the 16% elevation of HDL cholesterol noted in previously reported hypercholesterolemic patients.[13] Recent population studies[13, 14] have demonstrated that HDL cholesterol is powerfully and inversely related to risk of coronary heart disease. Moreover, studies of kindred and familial elevations of HDL cholesterol have documented reduced coronary artery morbidity and mortality and prolonged life spans.[15, 16] No broad epidemiologic studies of familial aggregation and HDL cholesterol have yet been reported. Females tend to have higher HDL levels than males, and blacks have higher levels than whites. Obesity has an inverse relationship with HDL cholesterol, and patients who are chronic cigarette smokers have lower HDL levels. Secondary elevations of HDL concentration have been documented with estrogenic preparations and low but regular alcohol consumption. In addition, middle-aged men taking regular exercise had higher HDL cholesterol levels than a sedentary control group.[17]

In the familial lipoproteinemias, there appears to be an inverse relationship between VLDL and HDL cholesterol such that increases in VLDL are associated with reduced HDL concentrations. No study has demonstrated a definite link between elevated VLDL lipoproteins (hypertriglyceridemia) and further progression of atherosclerosis. Perhaps triglyceride levels themselves are not inherently atherogenic but may be related inversely to HDL cholesterol. We found serum triglyceride levels in patients with elevated HDL cholesterol predominantly in the low normal range (*Fig. 3*). Our hypertriglyceridemia patients on the other hand had low normal or abnormally low HDL levels. Perhaps HDL cholesterol interacts with triglycerides such that when VLDL levels are elevated, the HDL cannot hydrolyze the increased VLDL triglyceride and consequently the levels are relatively low.[18] Naito et al[3] demonstrated a small but statistically significant inverse relationship between HDL phospholipid and triglyceride in the development of coronary disease and suggested that a low HDL phospholipid-triglyceride ratio may be considered a risk factor. These data add strength to the argument that it is the interaction between HDL cholesterol and triglycerides that may be important in the development of future atherosclerotic disease. The general trend in our patients with elevated triglyceride levels was low normal or low HDL cholesterol. If there is an association between hypertriglyceridemia and atherosclerosis it may be because the HDL cholesterol level in these patients is low and not because the triglycerides are high.

In all of our patients with hypertriglyceridemia except one, the serum triglyceride levels returned to normal with just dietary intervention, weight reduction, and a regular exercise program (*Fig. 1*). This is in accord with previous reports.[1]

3. *Families at high risk for hypercholesterolemia and early coronary disease can be identified without screening the general population and surveillance of these families is justified.* Studies of families reveal a greater frequency of hypercholesterolemia among first degree relatives of heart attack vic-

tims under age 60.[19] Indeed, 16%–21% of the progeny of myocardial infarction patients under age 50 have elevated cholesterol levels. We do not recommend routine screening of serum cholesterol and triglycerides in all children, but only in those with a family history of hyperlipidemia or cerebral or coronary artery disease in relatives under 50.

Atherosclerosis and coronary heart disease are major health problems in the United States and other industrialized nations. Although clinical manifestations usually become apparent in the fifth to sixth decades of life, the atherosclerotic process begins in childhood and probably has its roots in infancy. Therefore, the ability to prevent or delay the complications of atherosclerosis resides in the ability to alter environmental and genetic factors early in life. Key facets of this program are:

1. Instruction on rational intake of calories beginning in infancy and childhood, since long-term caloric imbalance with resultant obesity increases trends toward hypertension, hyperlipidemia, and hyperglycemia.

2. Instruction in proper nutrition, and avoidance of foods high in cholesterol and saturated fats.

3. Encouragement of high-energy physical activity in childhood to establish lifelong patterns of regular exercise.

4. Discouragement of smoking by abstention and cautioning children on its long-term effects.

The dual role of the clinician is to identify the children at highest risk, and to educate them regarding cardiovascular health. Most children with hypertriglyceridemia can attain normal triglyceride levels with proper diet, weight reduction, and exercise. In children with hypercholesterolemia, cholesterol levels can be reduced with diet and exercise, but some form of medical therapy will be necessary, especially in the homozygote hypercholesterolemic child who will probably need combination therapy. Children with elevated HDL cholesterol should be followed for years and the relationship between HDL cholesterol and triglyceride monitored carefully.

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