Management of Dyslipidemia in Children and Adolescents With Diabetes

AMERICAN DIABETES ASSOCIATION

Many studies have demonstrated that the atherosclerotic process begins in childhood in association with high blood cholesterol levels (1–3). Lipid levels show a strong familial aggregation that has both a genetic and environmental component (4). Monogenic disorders including familial hypercholesterolemia and familial combined hyperlipidemia are expressed in childhood, although adverse diet, polygenic disorders, and environmental causes (including obesity) are the most common causes of high cholesterol levels in children.

Adult patients with diabetes are at significant risk for cardiovascular disease (CVD). Because the combination of diabetes and dyslipidemia accelerates atherogenesis, aggressive lipid management is suggested for such patients (5). While the American Diabetes Association has stated lipid goals for adults with diabetes (6), no similar guidelines exist for children. To address this issue, a panel of experts in the areas of pediatric endocrinology, pediatric cardiology, and pediatric nephrology met on the 28th and 29th of July 2002 to hear presentations, review current lipid guidelines for children in general, and formulate a set of recommendations regarding the lipid management of children with diabetes. The panel was asked to develop a consensus position on the following questions:

1) Are there specific lipid abnormalities documented in children with diabetes?

2) Do lipid levels track from childhood to adulthood?

3) Does atherosclerosis begin in childhood? Is this related to dyslipidemia?

4) What is the frequency for monitoring lipid levels in children with diabetes?

5) How should elevated lipid levels be treated?

6) What additional research needs to be done in this area?

QUESTION 1: ARE THERE SPECIFIC LIPID ABNORMALITIES IN CHILDREN WITH DIABETES?

There are insufficient data available to answer this question. Most reviews speculate that the abnormalities seen in adults with diabetes are also seen in children/adolescents. In children with type 1 diabetes, the pathogenesis of the disease would not suggest the presence of specific lipid abnormalities; however, elevated triglycerides would be expected in patients with poorly controlled blood glucose levels. The Pittsburgh Diabetes Clinic found differences between diabetic patients and their siblings in an HDL subfraction, but other lipid levels were not significantly different (7).

In children with type 2 diabetes, the patterns seen in adults with type 2 diabetes, i.e., elevated triglycerides, normal to slightly elevated LDL cholesterol levels (with an increase of the small, dense LDL subfraction), and decreased HDL cholesterol levels (8,9) are also seen. Because severe obesity is associated with the premature onset of type 2 diabetes in adolescence and dyslipidemia is generally found in overweight/obese children, the coexistence of both risk factors should be expected and may contribute to dyslipidemia (10). Since obesity and dyslipidemia are part of the "metabolic syndrome," as defined by the third report of the National Cholesterol Education Program Adult Treatment Panel (NCEP/ATP III) (5), childhood obesity is seen as a risk factor for development of the syndrome in adulthood (11–13).

QUESTION 2: DO LIPID LEVELS TRACK FROM CHILDHOOD TO ADULTHOOD?

Children and adolescents with high cholesterol levels are more likely than the general population to have high levels when they become adults (14,15). In the general population, total cholesterol levels are generally 40 mg/dl higher in adults than in childhood. While most children with high cholesterol levels will also have high levels as adults, some children with high levels will have normal levels as young adults. This is in part related to the dramatic decrease in total cholesterol seen as children progress through puberty (16). Data from the Bogalusa Heart Study (1) and the Muscatine study (14), however, clearly show that cholesterol and other cardiovascular risk factors often persist from childhood to adulthood. For example, the development of obesity in childhood predicts a similarly elevated weight as an adult. The tracking correlation coefficients for dyslipidemia suggest that most but not all children with lipid abnormalities will have them as adults (14).

QUESTION 3: DOES ATHEROSCLEROSIS BEGIN IN CHILDHOOD? IS THIS RELATED TO DYSLIPIDEMIA?

Autopsy studies demonstrate that aortic and coronary atherosclerosis are commonly seen before age 20 years (1–3). High serum total cholesterol, LDL cholesterol, very-low-density lipoprotein (VLDL) cholesterol levels, and low HDL cholesterol levels are correlated with the extent of early atherosclerotic lesions in adolescents and young adults. For example, in the Bogalusa studies, antemortum total and LDL cholesterol levels, blood pressure, BMI, and fasting insulin were all positively correlated with aortic and cor-

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Abbreviations: AHA, American Heart Association; CVD, cardiovascular disease; LFT, liver function test.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

onary artery fatty streaks and plaques (1,2). The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study (3) reported that LDL cholesterol, severe obesity, and elevated glycohemoglobin levels were significantly correlated with the postmortem diagnosis of coronary atherosclerosis in 15- to 35-year-olds (17). In the Muscatine study (18), increased BMI and blood pressure and decreased HDL correlated with the early development of coronary calcification, considered a marker for atherosclerosis. The prevalence of coronary calcium in adolescents with familial hypercholesterolemia is ~25%, and the presence of calcium is more likely in those with the highest BMI (19).

Identified risk factors contributing to the early onset of CHD in children/adolescents include (20):

- Elevated LDL
- Family history of premature (aged <55 years) coronary heart disease, CVD, or peripheral vascular disease
- Smoking
- Hypertension
- HDL <35 mg/dl
- Obesity (≥95th percentile weight for height on National Center For Health Statistics (NCHS) growth chart)
- Physical inactivity
- Diabetes

QUESTION 4: WHAT IS THE FREQUENCY FOR MONITORING LIPID LEVELS IN CHILDREN WITH DIABETES?

As noted in Table 1, monitoring should closely follow recommendations currently made for children in general (20–23). That is, lipid levels should be measured initially in children (>2 years of age) only in the presence of a positive family history (a parental total cholesterol level ≥240 mg/dl and/or a cardiovascular event in a parent before age 55 years). The preferred test is the fasting lipid profile. In children with diabetes, we recommend modifications in this protocol based on the type of diabetes and the age of the child.

Type 1 diabetes

In those >12 years of age (assumed to be pubertal), screening should be done at diagnosis but after glycemic control is achieved and should be repeated every 5 years if the initial screen is normal.

In those <12 years of age (generally prepubertal), in the absence of a parental history of dyslipidemia or early coronary heart disease, there is no clear indication for a screening lipid exam.

Table 1—*Management of dyslipidemia in children/adolescents with diabetes*

Screening
After glycemic control is achieved
Type 1
Obtain lipid profile at diagnosis and then, if normal, every 5 years
Begin at age 12 years (or onset of puberty, if earlier)
Begin prior to age 12 years (if prepubertal) only if positive family history
Type 2
Obtain lipid profile at diagnosis and then every 2 years
Goals
LDL <100 mg/dl
HDL >35 mg/dl
Triglycerides <150 mg/dl
Treatment strategies
Diet
Maximize glycemic control
Weight reduction, if indicated
Medications
Age >10 years
LDL ≥160 mg/dl
LDL 130–159 mg/dl: consider based on CVD risk profile
Statins ± resins
Fibric acid derivatives if triglycerides >1,000 mg/dl
Manage other CVD risk factors
Blood pressure
Tobacco
Obesity
Inactivity

Type 2 diabetes

Children should be screened at diagnosis regardless of age but after glycemic control is achieved. If normal lipid values are obtained, screening should be repeated every 2 years.

Optimal lipid levels for children with diabetes are based on a synthesis of current pediatric recommendations and current recommendations for adults with diabetes, which recognize that the presence of diabetes is now considered a coronary heart disease equivalent (5,20–23). Optimal lipid levels for those with diabetes, as defined here and noted in Table 1, are in accord with those of the Third Adult Treatment Panel (5) and the American Heart Association (AHA) (23):

- LDL <100 mg/dl
- HDL >35 mg/dl
- Triglycerides <150 mg/dl

QUESTION 5: HOW SHOULD ELEVATED LIPID LEVELS BE TREATED?

Treatment recommendations, as noted in Table 1, are similar to established pediatric guidelines (20–23) with modifications in response to the higher CVD risk status of patients with diabetes. For children in general, "borderline" levels of total cholesterol and LDL are defined as 170–199 and 110–129 mg/dl, respectively. "Elevated" levels are >200 mg/dl for total cholesterol and >130 mg/dl for LDL cholesterol.

Whereas previous recommendations (20,21) suggested a progression from AHA step 1 to step 2 diet utilization, more recent recommendations suggest the use of the AHA step 2 diet (dietary cholesterol <200 mg/day and saturated fat <7% of total calories) initially upon confirmation of hyperlipidemia (23). Drug therapy has been recommended in children >10 years of age if, after an adequate trial of dietary therapy, LDL levels remain ≥190 mg/dl in those with no CVD risk factors or >160 mg/dl in those with CVD risk factors, such as a positive family history, hypertension, obesity, and diabetes (20,21). The goal LDL is <130 mg/dl for children

in general and <100 mg/dl in those with diabetes (23).

Based on the above considerations, the panel recommends the following for children and adolescents with lipid values greater than the optimal levels, as noted above.

1) Blood glucose control should be maximized and dietary counseling should be provided. Dietary change has been documented to reduce LDL levels (24). The use of products such as Benachol margarine and increasing amounts of soluble fiber should be considered as part of the dietary approach. Follow-up fasting lipid profiles should be performed at 3 months and then at 6 months to determine the effects of blood glucose management and dietary change. If treatment goals are achieved, the lipid profile should be repeated yearly. If after 6 months of optimized blood glucose control and dietary intervention there is no significant improvement in lipid parameters, further intervention is warranted based on LDL levels shown below:

- LDL 100–129 mg/dl: maximize nonpharmacologic treatment.
- LDL 130–159 mg/dl: "consider" medication, basing the treatment decision on the child's complete CVD risk profile, including assessment of blood pressure, family history, and smoking status.
- LDL ≥160 mg/dl: begin medication.

2) Resins (bile acid sequestrants) continue to be generally recommended as first-choice treatments in this age group; however, compliance rates with this class of medications are so low that therapeutic efficacy is lacking. Therefore, statin drugs should also be considered. Despite concerns about using statins in children, there are now trial data indicating efficacy and safety in adolescents (25,26). When statins are used, treatment should begin at the lowest available dose and dose increases should be based on LDL levels and side effects. Liver function tests (LFTs) should be monitored and medication should be discontinued if LFTs are greater than three times the upper limit of normal. If there is any persistent complaint of significant muscle pain/muscle soreness, the medication should be discontinued to see if symptoms resolve. Routine monitoring of creatine phosphokinase levels is not felt to be helpful. In addition, the use of statins in sexually active adolescent females must be very carefully considered and the risks explicitly discussed, as these drugs are not approved in pregnancy.

3) Elevated triglyceride levels are not directly managed with medication. If the tryglyceride level is ≥150 mg/dl, one should enhance efforts to maximize blood glucose control and achieve desirable weight. If triglycerides are ≥1,000 mg/dl, significantly increased risk of pancreatitis is present, and treatment with a fibric acid medication should be considered.

4) The cardiovascular risk approach to children with diabetes should be comprehensive. Thus, blood pressure should be regularly measured, anti-tobacco counseling provided, physical activity encouraged, and obesity managed (8,9,22,23).

QUESTION 6: WHAT ADDITIONAL RESEARCH NEEDS TO BE DONE IN THIS AREA?

Important research questions

The panel identified a number of critical areas of research:

- Longitudinal tracking of lipid levels in children with type 1 and type 2 diabetes are needed, as well as studies regarding the relationship of glycemic control and exercise to lipid levels.
- Studies are needed on the transition from obesity or insulin resistance to the onset of type 2 diabetes to determine at what point dyslipidemia occurs. Particularly important is an understanding of whether dyslipidemia precedes or is coincident with glucose intolerance.
- Understanding the relationship of noninvasive markers of end organ injury (carotid intimal medial thickening, coronary calcification, flow-mediated vascular resistance, and vascular compliance) to insulin resistance and type 2 diabetes would be helpful.
- The association of hyperlipidemia with other diabetes complications, particularly the development of microalbuminuria, should be addressed.
- The influence of diet on hyperlipidemia and the treatment of obesity (specifically high- versus low-carbohydrate diets) needs clarification.
- The influence of demographic characteristics (e.g., race, gender) on the prognosis of abnormal lipid levels should be studied.

APPENDIX

Consensus panel members

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