Prevention of Future Cardiovascular Disease in High-Risk Pediatric Patients
A Role for Lipid Lowering Therapy?

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Over the past 3 decades, childhood obesity has increased dramatically and has been deemed an epidemic by the Centers for Disease Control and Prevention.1 The 2002 National Health and Nutrition Examination Survey reported that the prevalence of overweight and obese children aged 6 to 19 years was 31%, a 45% increase from the previous survey.2 Obesity has been linked to comorbid conditions in children, including type 2 diabetes mellitus, hypertension, and hyperlipidemia.3,4 There is widespread concern that the increasing prevalence of these cardiovascular risk factors in the pediatric population will lead to a dramatic rise in adult cardiovascular disease. However, because of the difficulty associated with conducting long-term longitudinal studies necessary to validate these concerns, most investigations in this area, to date, have focused on the relationship between childhood obesity and surrogate markers of cardiovascular disease. The presence of obesity, hyperlipidemia, and hypertension in childhood has been linked to elevated left ventricular mass and carotid intima-media thickness, as well as peripheral endothelial dysfunction.4–7 These have been shown to be markers of cardiovascular risk in adult patients.8–10 Other studies have shown that childhood obesity and associated comorbidities are related to early atherosclerosis. In an autopsy series, Berenson et al11 showed that the presence and severity of coronary atherosclerotic plaque in asymptomatic young adults was significantly related to the number of risk factors present, including higher body mass index, hypertension, and hyperlipidemia. A recent Danish study is the first to demonstrate a link between childhood obesity and cardiovascular events in adulthood. Baker et al12 identified 275,835 adults for whom there was information on childhood body mass index and found that childhood body mass index was significantly associated with coronary artery events and death in adulthood.12

In light of these findings, the American Academy of Pediatrics (AAP) recently issued a statement on lipid screening and cardiovascular health in childhood.13 The AAP recommended routine lipid screening beginning at age 2 in high-risk pediatric patients, including those with cardiovascular disease risk factors such as overweight, obesity, hypertension, cigarette smoking, and diabetes mellitus, or a family history of dyslipidemia or premature cardiovascular disease. Lifestyle modification, including changes in diet and exercise habits, is recommended as first-line therapy for pediatric patients with dyslipidemia. However, if this approach does not lower low-density lipoprotein (LDL) to acceptable levels, pharmacological therapy is recommended in patients who are ≥8 years of age.13

While it is certain that the increases in childhood obesity and associated comorbidities are major public health concerns, there are little data to guide clinical decision-making regarding primary prevention in pediatric patients, particularly in relation to pharmacological therapy. As outlined in the AAP statement, there have been several short-term trials conducted recently evaluating the safety and efficacy of lipid-lowering agents in the pediatric population. These studies have established that several medications in the bile-acid binding resin, 3-hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitor (statin), niacin, and fibric acid derivative classes are effective lipid-lowering agents in pediatric patients.14–27 However, there are several important limitations to these studies. First, the sample sizes are relatively small, and only patients with familial hypercholesterolemia were included.14–27 Efficacy and safety in other high-risk pediatric patients have not been evaluated. In addition, although the AAP recommends pharmacological therapy for children as young as 8 years, only 1 study, to date, has included 8-year-olds. Pravastatin was studied in 214 patients with familial hypercholesterolemia aged 8 to 18 years.25 Pravastatin significantly reduced LDL levels (−24.1%) and was associated with a trend toward regression in carotid intima-media thickness. Thus, pravastatin is the only lipid-lowering agent in any class of medications labeled for use in children as young as 8 years.

Second, studies of lipid-lowering agents in children, to date, have evaluated safety and efficacy only over the short term. There are no data to evaluate whether aggressive lipid lowering in pediatric patients will alter the risk for future cardiovascular events. Even in certain high-risk adult patients, lipid-lowering therapy has not been shown to reduce the risk for future cardiovascular events when used in primary prevention.28,29 Recent studies of statins in pediatric patients have shown improvements in measures of endothelial function and regression of carotid intima-media thickness associ-
ated with statin therapy.\textsuperscript{25,30} Although these are used as surrogate markers of cardiovascular risk in adults, some studies have shown that improvements in these measures through lipid-lowering therapy do not necessarily translate into a significant reduction in cardiovascular events.\textsuperscript{31,32} Therefore, although pharmacological agents may be effective in improving the lipid profile in pediatric patients, it is unclear whether this will lead to a reduction in future cardiovascular disease.

Another important limitation of lipid-lowering studies, to date, is the lack of adequate safety data. Although short-term safety has been evaluated in several studies, long-term data are lacking. Certain medications found to have unacceptable side effects even over the short term are not recommended for routine use in pediatric patients. For example, although niacin was found to be effective in lowering LDL and total cholesterol concentrations, elevation in hepatic transaminases can occur in more than one quarter of patients.\textsuperscript{27} Other medications have been found to have side effects which, although minor, have resulted in poor compliance in children. The bile-acid binding resins are an attractive therapeutic option in children because they do not have systemic side effects. However, because of the high prevalence of gastrointestinal side effects, compliance was low in a McCrindle et al\textsuperscript{16} study evaluating 2 different formulations of cholestyramine. The statins, which have been studied most extensively in pediatric patients, have generally been found to have an adequate safety profile in short-term studies. Elevations in hepatic transaminases, creatine kinase, and episodes of rhabdomyolysis have been rare, and problems with growth and sexual maturation have not been observed over the short term.\textsuperscript{19–25} However, the impact of statin use over decades on liver function, muscle development, somatic growth, and sexual maturation is unknown.

There have also been concerns raised in the adult literature regarding the association between statin use and an increased incidence of cancer. In an analysis of several large randomized clinical trials, investigators found a significant association between the magnitude of LDL lowering and incidence of cancer.\textsuperscript{33} This has led some to speculate whether the cardiovascular benefits of low LDL may in part be offset by an increased risk of cancer. In addition, randomized trials in adults have also suggested that statin use may be associated with impairments in cognitive function. Investigators studying 308 patients aged 35 to 70 years found small decrements with impairments in cognitive function. Investigators studied 208 patients aged 35 to 70 years found small decrements in cognitive function in the treatment group after 6 months of simvastatin therapy.\textsuperscript{34} Animal studies have also raised the possibility of adverse effects of statins on central nervous system development. This is an important consideration in children given that brain development and rewiring seems to continue through childhood and adolescence into early adulthood.\textsuperscript{35} Lovastatin was found to significantly affect growth and development of neuronal and astroglial cells in an in vitro model of developing human central nervous system cells.\textsuperscript{36} Lovastatin was also found to significantly reduce brain cholesterol in mice, which was associated with altered membrane function.\textsuperscript{37} The long-term effects of statin treatment on cognitive function in children remain unknown.

A newer class of medication has received much attention recently. Ezetimibe (Zetia), a cholesterol absorption inhibitor primarily used in combination with statins, has been shown to reduce LDL levels significantly in adults.\textsuperscript{38} The AAP recommended ezetimibe as a possible first-line therapeutic agent in children.\textsuperscript{13} A recent randomized study of 248 patients with familial hypercholesterolemia age 10–17 years found that those receiving combined simvastatin and ezetimibe therapy had greater reduction in mean LDL levels (−49.5%) compared to simvastatin monotherapy (−34.4%, P<0.01).\textsuperscript{39} However, in the recent ENHANCE (Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression) trial, ezetimibe in combination with simvastatin was evaluated in 720 adults, and investigators found no change in carotid intima-media thickness or cardiovascular events in the combined therapy group compared with simvastatin alone, despite decreases in LDL levels.\textsuperscript{38} These findings lead the American College of Cardiology and American Heart Association to reinforce current guidelines that recommend statins as first-line therapy.\textsuperscript{40} Recently, the European Medicines Agency decided not to recommend use of ezetimibe in combination with simvastatin (Vytorin) in children, citing “no significant therapeutic benefit over existing treatments.”\textsuperscript{41}

In summary, the epidemic of childhood obesity and associated comorbidities is a significant public health concern. However, there is little evidence to guide pediatricians regarding the initiation of pharmacological therapy as primary prevention for future cardiovascular disease in high-risk pediatric patients. The recent AAP recommendations appropriately focus on lifestyle modification including reduced fat intake, exercise, and awareness of lipid levels with screening focused on high-risk children. However, recommendations for pharmacological treatment must take into account the unknown risk/benefit profile for long-term use of lipid-lowering agents in children. Comprehensive studies evaluating both the safety and efficacy of these agents over the mid and long term are crucial to guide pediatricians in this important and growing public health arena.

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