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Cardiovascular risk assessment and cholesterol management in adolescents: getting to the heart of the matter

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Abstract

Purpose of review—Adolescence is a common time for the identification of cardiovascular disease risk factors, including elevated cholesterol. Guidelines for the detection and treatment of hypercholesterolemia differ for children and adults. This review highlights these differences and discusses special considerations for cholesterol management in the adolescent population.

Recent findings—Several longitudinal studies have confirmed that the number of cardiovascular risk factors present in adolescence, including elevated cholesterol, lead to atherosclerosis in adults. There is increased awareness that other chronic medical conditions, including diabetes, congenital heart disease, inflammatory diseases, and childhood cancer, can accelerate this process. There is a move to screen and treat more young patients with elevated cholesterol to prevent future cardiovascular disease. New markers of atherosclerosis are being used to quantify cardiovascular disease risk in adolescents in research populations. The safety and efficacy of several interventions, including drug therapy, is increasingly established.

Summary—Comprehensive cardiovascular risk assessment is important for adolescent health and includes assessment of family history and tobacco use along with measurement of body mass index and blood pressure. Additionally, cholesterol screening is recommended for overweight adolescents or those with an unknown family history and for all patients by the age of 20. Providers caring for adolescents should be familiar with both the pediatric and adult cholesterol screening and treatment guidelines as well as how common adolescent conditions affect cholesterol levels.

Keywords

adolescents; cardiovascular disease; preventive medicine; cholesterol

Introduction

Atherosclerotic cardiovascular disease (CVD) remains the leading cause of death in the United States (1) and is now also the most common cause of death worldwide (2). It is well established that atherosclerosis, the pathologic basis for CVD, begins in childhood and progresses into

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adulthood (3). The major modifiable risk factors for CVD – smoking, hypertension, hypercholesterolemia, diabetes, and obesity – often begin in early life as well (4). Several studies have found that the number of CVD risk factors present in individuals correlates with the severity of atherosclerosis in both children and young adults (5–7*). Abnormal cholesterol levels in particular are increasingly common in adolescents, affecting one in five youth ages 12–19 (8), and are associated with atherosclerosis in adulthood (9).

This paper will discuss CVD risk assessment and prevention in the adolescent population and will focus on cholesterol screening and management. Adolescence is a common time for the emergence of CVD risk factors as well as the establishment of behavior patterns that affect CVD development and progression. Obesity, tobacco use, diabetes, hypertension, and hypercholesterolemia are all increasingly common in adolescence and some authors have predicted that the United States may see a reduction in life expectancy due to these trends (10). However, estimating the lifetime risk of a cardiovascular event for young individuals remains difficult because traditional tools only estimate the risk of an event in the next decade (11*). Furthermore, guidelines for the identification and treatment of hypercholesterolemia, a major modifiable risk factor for CVD, differ for children and adults. Providers caring for adolescents need to be aware of these differences and be able to provide comprehensive cardiovascular risk assessment for this population.

Since Kohn and Jacobson's article on cardiovascular risk in adolescents was published in this journal in 2004 (12), there have been revisions of both the pediatric and adult cholesterol screening and treatment guidelines (13**,14). In addition, there have been advancements and new controversies regarding the assessment of cardiovascular risk with novel biomarkers and imaging modalities (15**). This paper will review the changes in recommendations for lipid management in adolescents as well as discuss the discrepancies between pediatric and adult guidelines. It will also highlight conditions and illnesses common in adolescence that affect both lipid levels and treatment goals. Finally, tools for assessing, preventing, and treating CVD risk factors in adolescents will be discussed.

Guidelines for the detection and treatment of hypercholesterolemia in adolescents

In 2008 the American Academy of Pediatrics (AAP) Committee on Nutrition issued the policy statement "Lipid Screening and Cardiovascular Health in Childhood" (13**). These guidelines replaced those last issued in 1998 (16) and reflected emerging data from several cohort studies on cumulative cardiovascular risk from childhood into adulthood (5,6,17). The 2008 guidelines expanded the indications for cholesterol screening, endorsed fasting lipid profiles for all individuals, reduced the age (and in the case of those with diabetes, the LDL levels) at which pharmacologic intervention should be considered, and added several classes of acceptable lipid lowering medications. The expansion of pharmacologic options in particular sparked significant controversy within the pediatric and lay communities (18).

The AAP policy statement refers providers treating patients older than 18 to the Adult Treatment Panel (ATP) guidelines from the National Cholesterol Education Program, although these are actually designed for individuals ages 20 and older. The ATPIII guidelines published in 2002 focus on the importance of LDL cholesterol to cardiovascular health and the modification of LDL cholesterol according to overall risk of CVD (19). An update of ATPIII was published in 2004 prompted by emerging trial data that supported the lowering of LDL cholesterol even further for adults at moderate to high risk of CVD (14). These lower LDL goals will likely be incorporated into the ATPIV recommendations due for release in 2010.

Providers caring for older adolescents and young adults need to understand the differences between the pediatric and adult guidelines (Table 1) and be able to apply both as their patients age. Key areas of difference are the screening interval, the LDL treatment goals, and the use of CVD risk projection to alter those treatment goals. Notably the guidelines recommend more frequent lipid screening in adolescents as compared to adults but a higher LDL level at which to begin treatment. While elevated cholesterol levels in adolescence are known to track into adulthood, their sensitivity and specificity for elevated cholesterol levels in adulthood remain low at around 40% and 80% respectively (20). This corresponds to high false negative rates, which can be partially addressed by more frequent screening, and high false positive rates, which can be addressed by higher thresholds for treatment (21).

Cholesterol screening in adolescence is particularly challenging for several reasons. First, there are significant changes in lipid concentrations during puberty (22**). HDL levels decline in males throughout puberty while total and LDL cholesterol decline in early puberty but rise again as males approach adulthood. In contrast, total and LDL cholesterol rise throughout puberty in females while HDL levels stay essentially the same. Second, adolescents often present to clinic unaccompanied and may be unaware of a family history of elevated cholesterol. Finally, adolescents may be unlikely to return for fasting lipid profiles, currently the screening test recommended by the AAP. Fortunately, a recent study in adults found nonfasting total and HDL cholesterol were as strongly associated with CVD as fasting levels or directly measured LDL cholesterol (23*). Given these findings, we recommend obtaining a nonfasting total and HDL cholesterol for all adolescents with risk factors or unknown family history, preferably before the onset of puberty or if not, in late adolescence. If the initial nonfasting levels are elevated, a fasting lipid panel should be pursued. All patients should have a screening total and HDL cholesterol assessment by the age of 20.

Special populations and considerations

The 2008 AAP recommendations are targeted to all children and adolescents, but special consideration is necessary for patients with other conditions associated with accelerated atherosclerosis. While most practitioners are aware of the increased risk for CVD in patients with familial hypercholesterolemia, they may be less familiar with the risk incurred by diabetes mellitus, chronic kidney disease, chronic inflammatory diseases, congenital heart disease, and childhood cancer survivorship. In 2006 the American Heart Association released a scientific statement endorsed by the AAP defining the increased risk for CVD in these groups and recommending comprehensive cardiovascular assessment and treatment strategies for those affected by these conditions (Table 2) (24). Conditions are divided into those conferring the highest risk (Tier I), a moderately-increased risk (Tier II), or an increased risk (Tier III) for CVD. Patients with Tier II or III conditions who have 2 or more additional cardiovascular risk factors should be treated to the goals of the lower Tier. This is consistent with the adult guidelines' recommendation for alteration of lipid goals based on the number of cardiovascular risk factors present (19).

In addition to these relatively uncommon conditions which accelerate atherosclerosis, providers need to be aware of common adolescent conditions which can alter lipid levels and cause secondary dyslipidemia (Table 3). Hypothyroidism, both subclinical and overt, is associated with increases in total and LDL cholesterol and decreases in HDL cholesterol due to alteration in liver metabolism of these molecules (25). Screening for thyroid dysfunction with a TSH is recommended for all patients with dyslipidemia by the adult guidelines (19), and while not mentioned by the pediatric guidelines it is a reasonable approach in adolescents. Treatment with thyroxine improves lipid panels and is recommended for overt hypothyroidism but debated for those with subclinical disease. Anorexia nervosa, another illness commonly presenting in this age group, is also associated with increased total and LDL cholesterol. This

is likely due to the presence of excess cortisol, reduced free thyroxine, and increased lipolysis seen in these patients (26). Weight gain has been demonstrated to normalize the cholesterol abnormalities seen in patients with anorexia (27).

Medications used by adolescents are also associated with alterations in the lipid profile. The most common are oral contraceptive pills (OCPs) and injectable contraceptives, which have shown mixed effects (28*). In general estrogens increase triglycerides and HDL cholesterol while lowering LDL cholesterol, while progestins have the opposite effect. The advent of less androgenic progestins has lessened the rise in LDL cholesterol seen in earlier OCP formulations but the overall net effect continues to be a slight rise in all aspects of the lipid panel (29*). While not as commonly prescribed as OCPs, there is increasing use of atypical antipsychotics to treat adolescents with bipolar disease and psychotic disorders, and olanzapine and clozapine in particular can cause significant increases in triglyceride levels independent of their associated weight gain (30*). It is helpful to get a baseline lipid assessment before starting either OCPs or antipsychotics in adolescents. If a change in the lipid profile is detected after the initiation of drug therapy, the magnitude and risk of the increase must be weighed against the necessity of the drug. Finally, alcohol can raise both HDL cholesterol and triglycerides (31) and excess use or binge drinking should be considered in adolescents with isolated hypertriglyceridemia.

Treatment

Lifestyle modification is the mainstay of treatment for adolescents with CVD risk factors. The most recent American Heart Association guidelines recommend all teens eat fruits and vegetables daily, use whole-grain breads and nonfat or low-fat milk products, reduce their intake of sugar-sweetened beverages and salt, prepare foods with vegetable oils and margarines low in saturated fats, and eat minimal to no trans-fats (32). Adolescents with elevated lipid levels should adhere to a diet that restricts saturated fat to 7% of total calories and dietary cholesterol to 200mg per day and that includes supplemental fiber at a dose of the patient's age plus 5g per day, or 20g per day for those over age 15. The safety and efficacy of these recommendations was established by the Dietary Intervention Study in Children (DISC), which found a 4.8mg/dL reduction in LDL after one year in children randomized to a low fat diet and found no difference relative to controls with respect to height or sexual maturation over seven years of follow-up (33). Physical activity should also be increased to sixty minutes per day and weight reduced if the adolescent is overweight or obese. Motivational interviewing techniques may be helpful when counseling adolescents regarding lifestyle change (34*). All of these recommendations are consistent with adult guidelines for those patients over age 18 (19).

For adolescents who do not meet their LDL goal through a trial of therapeutic lifestyle changes (TLC), pharmacologic treatment is warranted, although adherence can be a challenge in this population (35*). While the pediatric guidelines do not define the time for trial of TLC, six months is a reasonable trial with an extension if the patient is having some success. Adolescents were historically treated with bile acid binding resins, but up to 50% of teens studied stopped the drugs due to poor palatability and gastrointestinal side effects (36). The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or statins, are now arguably the first-line treatment in adolescents with elevated LDL cholesterol. Multiple trials have demonstrated the safety and efficacy of statins in adolescents (37) and the most recent pediatric guidelines recommend their use in children as young as 8 years of age (13). Importantly, growth and pubertal maturation do not appear to be affected by statin use (38) although subtle effects cannot be excluded by the current published data. Although there is emerging data on the use of ezetimibe in this population (39*) its efficacy has recently been questioned in adults (40) and therefore statins remain the preferred drug for elevated LDL. All adolescent females should be counseled on the teratogenic effects of statins and their contraindication in pregnancy, and

appropriate birth control methods should be used for sexually active teens. Given the rare side effects of hepatic toxicity and rhabdomyolysis, the AHA recommends baseline measurement of CK, ALT and AST before initiation of statin therapy (37). Our practice is to measure efficacy and side effects initially monthly and then every 6 months. It is important to note that while the efficacy of statins for preventing first cardiovascular events is well-established in adults (41), the same is not true for the adolescent population. However, trials that would support such an assertion are unlikely to be performed given the large sample size and long follow-up necessary.

Treatment goals for elevated triglycerides and low HDL are not well-defined in the pediatric guidelines (13). Physical activity and weight reduction have been shown to increase HDL by 20–30% in adults and are recommended by the adult guidelines for patients with an HDL<40mg/dL (19). Drug therapy for an isolated low-HDL in adults is controversial and is not recommended for younger patients. Similarly, the adult guidelines (19) suggest TLC as the primary therapy for triglycerides in the borderline (150–199mg/dL) and high (200–499mg/dL) range. Drug therapy with either a statin if the patient's LDL is not at goal or a fibrate or nicotinic acid if the LDL is at goal may be considered for adults with high triglycerides that do not improve with TLC. Initiating triglyceride lowering therapy with a fibrate is suggested for very high levels >500mg/dL to prevent triglyceride-associated pancreatitis. It is reasonable to apply these guidelines to adolescents, and fibrates have been well tolerated by adolescents in at least one study (42). However, niacin is not recommended in this age group due to its high adverse event rate and bothersome cutaneous flushing (43). Dietary changes and physical activity have been shown to benefit adolescents with high triglycerides and low HDL (44,45) and remain the mainstay of treatment for these lipid abnormalities in both children and adults.

A recent survey by the Centers for Disease Control found 16% of adolescents use complementary or alternative therapies (46) and patients may inquire about those advertised to promote cardiovascular health. There is some data for the ability of naturally occurring substances such as plant sterols (47), omega-3 and -6 fatty acids (48*), soy products (49), and red rice yeast (50*), but not garlic (51), to lower cholesterol and cardiovascular risk. At least one study in adults found a similar level of LDL reduction to statins in those treated with multiple alternative therapies at once (52). While few of these studies have been done in adolescents, the products are generally well tolerated. Such complementary therapies can be used in adjunct with TLC or in adolescents with borderline cholesterol levels, but should not replace pharmacologic treatment with statins or bile acid resins for those teens at greatest cardiovascular risk.

New directions in cardiovascular risk assessment

Elevated cholesterol is only one risk factor for cardiovascular disease. Comprehensive CVD risk assessment includes annual assessment of blood pressure, BMI, tobacco use and family history of CVD as well as screening for diabetes when indicated. The Pathological Determinants of Atherosclerosis in Youth (PDAY) group has created a cardiovascular risk score comprised of these various risk factors for adolescents and young adults (53). Although not in clinical use at present, the PDAY offers an interesting new possibility for assessing lifetime risk of CVD in youth. Noninvasive markers of atherosclerosis such as ultrasonography of carotid intima-medial thickness (CMT) and computed tomography of coronary artery calcification (CAC) are also used in research settings with adolescents (54). While both have been associated with actual CVD outcomes in adults (55), a recent US Preventative Services Task Force review concluded there was insufficient evidence to endorse the use of either of these modalities over traditional risk factor assessment in adults (15). C-reactive protein (CRP) has also received considerable attention in the adult CVD literature (56*) and does appear to add additional information beyond traditional risk factor assessment in adults (15). The

association between high CRP in youth and atherosclerosis in adulthood is less clear (57,58) and CRP does not appear to be as tightly correlated with CVD risk factors other than obesity in this age group (59). Measurement of CRP in adolescents for the purpose of CVD assessment is not currently recommended outside of the research arena, given the general lack of data at this time. The soundest evidence in both adolescents and adults remains for comprehensive cardiovascular risk assessment based on the traditional risk factors of age, gender, family history, BMI, blood pressure, cholesterol, and glucose.

Conclusion

Atherosclerosis begins in childhood. Adolescence presents a prime opportunity to assess risk factors for cardiovascular disease and to intervene to prevent its development. Comprehensive cardiovascular risk assessment includes inquiry regarding family history and tobacco use along with measurement of body mass index and blood pressure. Lipid profiles should be obtained in adolescents with a positive or unknown family history or with any other CVD risk factors including obesity, and in all patients by the age of 20. Clinicians caring for adolescents should be aware of new recommendations from the American Academy of Pediatrics and the Adult Treatment Panel of the National Cholesterol Education Program and be able to apply both as patients transition to adulthood. Adolescents with diabetes, chronic inflammatory diseases, a history of childhood cancer, or congenital or acquired heart disease require special consideration and more aggressive cardiovascular risk management. Several conditions common in adolescence, including the use of alcohol or combined hormonal contraception and thyroid and eating disorders, can also affect lipid levels and cardiovascular risk. Clinicians should be able to counsel all patients regarding lifestyle modifications to prevent CVD and use pharmacologic treatment when necessary to improve lipid profiles. Early identification and intervention in childhood and adolescence is necessary to prevent morbidity and mortality from the lifetime risk of cardiovascular disease in adulthood.

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Table 1
Comparison of Pediatric (13) and Adult (19) Guidelines for Cholesterol Screening and Management

Italics are used to highlight differences between the pediatric and adult guidelines.

	AAP	ATP III
Screening	Recommended if family history of CVD or elevated cholesterol, if family history unknown, or if other CVD risk factors	Recommended for <i>everyone starting at age 20</i>
	Fasting lipid profile recommended	<i>Nonfasting total cholesterol and HDL recommended for low risk patients</i> ; fasting lipid profile recommended if 2 or more CVD risk factors
	If levels acceptable, repeat every 3 to 5 years	If levels acceptable and patient is low risk, repeat <i>every 5 years</i> ; if patient has 2 or more CVD risk factors, <i>repeat every 2 years</i>
Management	Dietary treatment with saturated fat <7%, dietary cholesterol <200mg/day, and fiber intake equal to age plus 5g/day (up to 20g/day)	Dietary treatment with saturated fat <7%, dietary cholesterol <200mg/day, <i>fiber intake 20–30g/day and plant sterols 2g/day</i>
	High triglycerides: weight management and exercise for overweight or obese patients	High triglycerides: weight management, exercise, <i>smoking and alcohol cessation if <200mg/dl; consider drug therapy if 200–499mg/dl; initiate drug therapy if >500mg/dl</i>
	Low HDL: weight management and exercise for overweight and obese patients	Low HDL: weight management, exercise, and <i>smoking cessation</i>
	LDL: Consider pharmacologic therapy if >190mg/dl or >160mg/dl and any other risk factors or LDL>130mg/dl and diabetes	<ul style="list-style-type: none"> 0–1 CVD risk factors: Pharmacologic therapy if LDL >190mg/dl, <i>consider if >160mg/dl</i> 2 or more CVD risk factors and 10 year CVD risk <10%: Pharmacologic therapy if LDL>160mg/dl 2 or more CVD risk factors and 10 year CVD risk >10%: Pharmacologic therapy if LDL>130mg/dl Diabetes: Consider pharmacologic therapy if LDL>100mg/dl
	Statins and bile acid sequestrants recommended	Statins recommended; bile acid sequestrants reasonable alternative in young patients; <i>nicotinic acid and fibrates useful as second line</i>

Table 2
American Heart Association Guidelines for Cardiovascular Risk Reduction in High-Risk Pediatric Patients (24)

Patients with Tier II conditions who have 2 or more additional cardiovascular risk factors should be treated to Tier I treatment goals. Patients with Tier III conditions who have 2 or more additional cardiovascular risk factors should be treated to Tier II treatment goals.

	Tier I	Tier II	Tier III
Diseases	Homozygous FH Type 1 Diabetes End stage renal disease S/P orthotopic heart transplantation Kawasaki disease with current coronary artery aneurysms	Heterozygous FH Type 2 Diabetes Chronic inflammatory disease Kawasaki disease with regressed coronary aneurysms	Congenital heart disease Cancer treatment survivors Kawasaki disease without coronary involvement
Treatment Goals	BMI<85%ile for age/sex BP<90%ile for age/sex/ht LDL cholesterol <100mg/dl FG<100mg/dl, HbA1C <7%	BMI<90%ile for age/sex BMI<95%ile for age/sex/ht LDL cholesterol <130mg/dl FG<100mg/dl, HbA1C <7%	BMI<95% for age/sex BMI<95%+5mmHg for age/sex/ht LDL cholesterol <160mg/dl FG<100mg/dl, HbA1C <7%

Table 3
Conditions associated with secondary dyslipidemia in adolescents

Hypothyroidism
Anorexia Nervosa
Drugs (estrogens, progestins, anabolic steroids, corticosteroids, protease inhibitors, oral retinoids)
Alcohol
Diabetes mellitus
Chronic renal failure or nephritic syndrome
Liver failure