Screening for Lipid Disorders in Children

United States Preventive Services Task Force

Recommendation Statement

Summary of Recommendation

The USPSTF concludes that the evidence is insufficient to recommend for or against routine screening for lipid disorders in infants, children, adolescents, or young adults (up to age 20)**. (**I recommendation)

Rationale

Importance: There is good evidence that children with lipid disorders (dyslipidemia) are at risk for becoming adults with lipid disorders.

Detection: For children with familial dyslipidemia, the group most likely to benefit from screening, use of family history in screening may be inaccurate because of variability of definitions and unreliability of information. Serum lipid levels are accurate screening tests for childhood dyslipidemia, although many children with multifactorial types of dyslipidemia would have normal lipid levels in adulthood. Fifty percent of children and adolescents with dyslipidemia will have dyslipidemia as adults.

***Benefits of detection and early treatment:** Trials of statin drugs in children with monogenic dyslipidemia (defined below in clinical considerations) indicate improved total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) measures. For children with multifactorial types of dyslipidemia, there is no evidence that diet or exercise interventions in childhood lead to improved lipid profiles or better health outcomes in adulthood.

*= *critical evidence gap*

Harms of detection and early treatment: Potential harms of screening may include labeling of children whose dyslipidemia would not persist into adulthood or cause health problems, although evidence is lacking. Adverse effects from lipid-lowering medications and low-fat diets, including potential long-term harms, have been inadequately evaluated in children.

USPSTF assessment: The USPSTF was unable to determine the balance between potential benefits and harms for routinely screening children and adolescents for dyslipidemia.

Clinical Considerations

- Dyslipidemias are abnormalities of lipoprotein metabolism and include elevations in TC, LDL-C, or triglycerides or deficiencies of HDL-C. These disorders can be acquired or familial; monogenic dyslipidemias are related to genetic conditions such as familial hypercholesterolemia in some individuals. Multifactorial dyslipidemias are due to risk factors including environmental factors (obesity, diet) or currently unidentified genetic factors. This recommendation applies to all asymptomatic individuals from birth to age 20.

- Because abnormal lipid levels have been strongly associated with the risk of coronary heart disease (CHD) events in adulthood, and early identification and lipid-lowering intervention in certain populations of adults can prevent CHD events, much attention has been directed at screening individuals for dyslipidemia at young ages (eg, childhood). Among children and adolescents, 3 groups may be identified through screening: (1) children with undiagnosed monogenic dyslipidemias such as familial hypercholesterolemia; (2) those with undiagnosed secondary causes of dyslipidemia; and (3) those with multi-factorial dyslipidemia (polygenetic or related to risk-factors). However, the clinical health benefits shown in adults identified and treated for dyslipidemia have not been studied in children, making the role of screening children uncertain.

- Children and adolescents with diabetes may be at especially high risk for dyslipidemia and cardiovascular events. Screening children and adolescents with diabetes for dyslipidemia has been recommended by other groups as a part of appropriate care for these children.

- The use of family history as a screening tool for dyslipidemia has variable accuracy largely because definitions of a positive family history and lipid threshold values vary substantially. Screening using family history as defined by the National Cholesterol Education Program (NCEP) and the American Academy of Pediatrics (AAP) has been shown to have high rates of false negative results.

- If clinicians choose to screen for dyslipidemia, the preferred screening tests are TC and HDL-C on nonfasting or fasting samples; calculating LDL-C requires fasting samples.

Other Considerations

- Effectiveness of treatment interventions (diet, exercise, lipid lowering agents) in children with dyslipidemia (including multifactorial dyslipidemia) in improving health outcomes remains a critical research gap. Population-based screening studies or randomized controlled trials (RCTs) following children and adolescents into adulthood after treatment interventions will be necessary to assess universal lipid screening in childhood or adolescence.

- Rising rates of childhood overweight may lead to a higher prevalence of dyslipidemia in childhood and adulthood. Continued tracking of dyslipidemia in all age groups will be important as the epidemiology of obesity evolves.

Discussion

Epidemiology

Dyslipidemias are disorders of lipoprotein metabolism and include elevations in TC, LDL-C, or triglycerides, or deficiencies of HDL-C. TC levels increase from birth, stabilize at approximately 2 years of age, peak before puberty, and then decline slightly during adolescence. Normal values for lipids in children and adolescents are currently defined according to population distributions of lipid levels from the Lipid Research Clinics (LRC) Prevalence Study conducted in the 1970s.[1] Dyslipidemia is commonly defined as TC >200 mg/dL and LDL-C >130 mg/dL; these values correspond to the 95% percentile observed in the LRC study. More recent studies, including the National Health and Nutrition Examination Survey, indicate that age, sex, racial differences, and temporal trends shift these population-based cut points.[2]

Although dyslipidemia in adults is an established risk factor for CHD based on good quality evidence from long-term prospective studies, the CHD risk attributable to dyslipidemia during childhood is unknown. Indirect evidence from the Bogalusa Heart Study, a long-term epidemiologic study of risk factors for CHD from birth through 31 years of age, showed a correlation between lipid levels and arterial fat deposition seen at autopsy; however, such evidence does not directly link childhood lipid levels to health outcomes.[3] Epidemiologic studies in children establish a strong statistical association between childhood overweight and dyslipidemia.[2] Other risk factors for dyslipidemia include an established family history for common familial dyslipidemias including familial hypercholesterolemia, familial combined hypercholesterolemia, familial defective apoprotein B, and familial hypertriglyceridemia. Secondary causes of dyslipidemia include diabetes, nephrotic syndrome, and hypothyroidism.[2]

The USPSTF did not find direct evidence that screening for dyslipidemia leads to improvements in CHD-related mortality or overall mortality; therefore it reviewed the evidence on accuracy of screening tests including family history, efficacy of treatment, and harms of screening and treatment in children.

Accuracy of Screening Tests

TC and HDL-C can be measured on nonfasting venous or capillary blood samples, LDL-C measurement requires fasting samples, and direct LDL-C can be measured on nonfasting venous samples. At least two measurements are necessary to ensure that true values are within 10% of the mean of the measurements. Fair-quality evidence shows that a value of TC minus HDL-C above the 95th percentile is 88% to 96% sensitive and 98% specific for detecting LDL-C $\geq$130 mg/dL.[4,5,6] Although use of family history presents one potential method to target serum lipid screening to a group of children and adolescents with higher risk for dyslipidemia, its use is limited. Family history is time-consuming to elicit accurately, it has been variably defined in the literature, and its use as a screening tool has been shown to miss substantial numbers (30% to 60% in general) of children with elevated lipids. Family history definitions vary substantially among studies as do lipid detection thresholds; those studies that show higher sensitivities (~77%) have low specificities (≤55%).[2] Population-based estimates of the number of children requiring serum lipid testing based on positive family history may range from 25% to 55%, depending on definitions of family history and serum LDL cut-off values.

Accurate screening tests in children would be useful if childhood dyslipidemia correlated with adult CHD health outcomes or with adult dyslipidemia as an intermediate outcome and if treatment improved CHD outcomes. Serial correlations between lipid levels measured in individual children over time vary on the basis of the type of lipid level followed. On the basis of the evidence from 23 prospective cohort studies, correlations have been found to be higher for TC (r=0.38-0.78) and LDL-C (r=0.4-0.7), than for HDL-C (r=0-0.8) and triglyceride (r=0.1-0.58) levels, and good quality evidence indicates that approximately 40% to 55% of children with elevated TC and LDL will continue to have elevated lipids on followup into adolescence and early adulthood.[2] No studies examine tracking of lipids in those with risk factors for dyslipidemia (eg, childhood overweight).

Efficacy of Treatment

Treatment of childhood dyslipidemia has been shown to be effective in lowering lipid levels in select populations; however, no studies address the effect of treatment on childhood or adult health outcomes (eg, CHD events). In those children with diagnosed monogenic dyslipidemia, a condition that has been associated with premature CHD events, no RCTs are likely be completed to provide health outcomes in untreated controls. In this population of children with familial monogenic dyslipidemias (familial hypercholesterolemia or familial combined hyperlipidemia), good quality evidence based on a meta-analysis of nine RCTs demonstrates the effectiveness of statins in reducing intermediate outcomes: TC and LDL (percent mean reduction [95% confidence limits] from meta-analysis of trials: 24.4%[19.5, 29.2] for TC, 30.8% [24.1, 37.5] for LDL, in 8 studies).[2] Fair evidence based on two fair-quality trials shows that bile acid

binding resins reduce lipid levels in children with monogenic dyslipidemia.[7,8] RCTs of diet supplements (psyllium, oat, garlic extract, and sterol margarine) and advice show marginal improvements in lipids in children with monogenic dyslipidemia.[2] There is fair quality evidence that dietary counseling is associated with minimal improvements in lipid levels in children with monogenic and multifactorial dyslipidemias; however, these improvements may not be sustained after counseling intervention ceases.[9,10,11,12,13,14,15] There are no studies of physical activity interventions in those with monogenic dyslipidemia and fair-quality evidence in those with multifactorial dyslipidemia based on a meta-analysis of 6 trials that showed that physical activity interventions were associated with minimal to no improvement in lipid levels in children with multifactorial dyslipidemia (percent mean reduction [95% confidence limits] from meta-analysis of trials: 0% [-5.6, 5.6] for TC, and 3.1% [-7.7, 1.5] for LDL-C reduction in 4 studies). [2]

Harms of Screening and Treatment

There is poor-quality evidence on the adverse effects of screening. There are conflicting reports about behavioral difficulties in screened children and reports of parental noncompliance with recommendations for diet and followup. Studies have shown no increases in anxiety among screened children and adolescents.[2] Fair-quality evidence on the harms of treatment is based on 81 controlled and non-controlled studies of treatment that reported a variety of adverse effects of drug, diet, exercise, and combination therapy in children and adolescents.[2] Lipid-lowering agents have been shown to cause elevations in creatine kinase and liver function tests (statins), gastrointestinal side effects, and decreased absorption of vitamins and minerals (bile acid resins). The adverse effects of long-term use of lipid-lowering agents (eg, >20 years) have not been studied. There have been 3 reports of growth retardation and nutritional dwarfing in children on unmonitored diets; however there are several reports of normal growth during monitored low-fat diet interventions.[2] Physical activity interventions have had no reported harms in children without monogenic dyslipidemia, but an exaggerated blood pressure response was seen in children with monogenic dyslipidemias who were undergoing physical activity intervention.

Recommendations of Others

No professional organization recommends universal screening for dyslipidemia in children or adolescents. The NCEP Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents recommends selective screening for children and adolescents with a family history of premature CHD or at least 1 parent with a high TC level (TC $\geq$240 mg/dL) in the context of regular health care. Optional cholesterol testing may be recommended in children and adolescents judged to be at higher risk independent of family history or parental hypercholesterolemia (eg, those who are overweight or have high-fat diets).

The American Academy of Pediatrics' recommendations are based on this NCEP report and concur with its screening recommendations.[16] The American College of Obstetricians and Gynecologists concurs with the NCEP recommendations for screening in adolescents.[17] In 2003, the American Heart Association (AHA) recommended performing targeted screening of fasting lipids in children >2 years of age with a family history of dyslipidemia or premature cardiovascular disease and in those children for whom family history is unknown and other risk factors are present.[18] In a 2007 update, the AHA recommends, in addition, screening children who are overweight or obese.[19]

References

[1] The Lipid Research Clinics Program. *Population studies data book.v*ol I. The prevalence study. National Institutes of Health: National Heart, Lung, and Blood Institute. DHHS publication no. (NIH) 80-1527. Washington, DC: U.S. Government Printing Office, 1980.

[2]Haney EM, Huffman LH, Bougatsos C, et al. *Screening for lipid disorders in children and adolescents: systematic evidence review for the U.S. Preventive Services Task Force.* Evidence Synthesis Number 47. Prepared for the Agency for Healthcare Research and Quality (AHRQ) by the Oregon Evidence-based Practice Center, Portland, Oregon, under Contract Number 290-02-0024. AHRQ Publication No. 07-0598-EF-1. July 2007. Available at http://www.ahrq.gov/clinic/serfiles.htm.

[3] Freedman DS, Shear CL, Srinivasan SR, Webber LS, Berenson GS. Tracking of serum lipids and lipoproteins in children over an 8-year period: the Bogalusa Heart Study. *Prev Med.* 1985;14(2):203-216.

[4] Kwiterovich PO, Jr, Heiss G, Johnson N, Chase GA, Tamir I, Rifkind B. Assessment of plasma total cholesterol as a test to detect elevated low density (beta) lipoprotein cholesterol levels (type IIa hyperlipoproteinemia) in young subjects from a population-based sample. *Am J Epidemiol.* 1982;115(2):192-204.

[5] Shea S, Basch CE, Irigoyen M, et al. Failure of family history to predict high blood cholesterol among Hispanic preschool children. *Prev Med.* 1990;19(4):443-455.

[6] Dennison BA, Kikuchi DA, Srinivasan SR, Webber LS, Berenson GS. Serum total cholesterol screening for the detection of elevated low-density lipoprotein in children and adolescents: the Bogalusa Heart Study. *Pediatr.* 1990;85(4):472-479.

[7] McCrindle BW, O'Neill MB, Cullen-Dean G, Helden E. Acceptability and compliance with two forms of cholestyramine in the treatment of hypercholesterolemia in children: a randomized, crossover trial. *J Pediatr.* 1997;130(2):266-273.

[8] Tonstad S, Knudtzon J, Sivertsen M, Refsum H, Ose L. Efficacy and safety of cholestyramine therapy in peripubertal and prepubertal children with familial hypercholesterolemia. *J Pediatr.* 1996;129(1):42-49.

[9] Obarzanek E, Kimm SY, Barton BA, et al. Long-term safety and efficacy of a cholesterol-lowering diet in children with elevated low-density lipoprotein cholesterol: seven-year results of the Dietary Intervention Study in Children (DISC). *Pediatr.* 2001;107(2):256-264.

[10] DISC Collaborative Research Group. Efficacy and safety of lowering dietary intake of fat and cholesterol in children with elevated low-density lipoprotein cholesterol. The Dietary Intervention Study in Children (DISC). The Writing Group for the DISC Collaborative Research Group. *JAMA.* 1995;273(18):1429-1435.

[11] Shannon BS, Tershakovec AM, Martel JK, Achterberg CL, Cortner JA. Reduction of elevated LDL-cholesterol levels of 4- to 10- year-old children through home-based dietary education. *Pediatr.* 1994;6(6 Pt 1):923-927.

[12] Davidson MH, Dugan LD, Burns JH, Sugimoto D, Story K, Drennan K. A psyllium-enriched cereal for the treatment of hypercholesterolemia in children: a controlled, double-blind, crossover study. *Am J Clin Nutr.* 1996;63(1):96-102.

[13] McCrindle BW, Helden E, Conner WT. Garlic extract therapy in children with hypercholesterolemia. *Arch Pediatr Adol Med.* 1998;152(11):1089-1094.

[14] Amundsen AL, Ose L, Nenseter MS, Ntanios FY. Plant sterol ester-enriched spread lowers plasma total and LDL cholesterol in children with familial hypercholesterolemia. *Am J Clinl Nutr.* 2002;76(2):338-344.

[15] de Jongh S, Vissers MN, Rol P, Bakker HD, Kastelein JJ, Stroes ES. Plant sterols lower LDL cholesterol without improving endothelial function in prepubertal children with familial hypercholesterolaemia. *J Inherited Metab Dis.* 2003;26(4):343-351.

[16] National Cholesterol Education Program. Highlights of the report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. *Pediatr.* 1992;89(3):495-501.

[17] American College of Obstetricians and Gynecologists. *Health care for adolescents*. Washington, DC: American College of Obstreticians and Gynecologists; 2003.
[18] Kavey RE, Daniels SR, Lauer RM, et al. American Heart Association guidelines for primary prevention of atherosclerotic cardiovascular disease beginning in childhood. Circulation. 2003 Mar 25;107(11):1562-6.
[19]McCrindle BW, Urbina EM, Dennison BA, et al. Drug therapy of high-risk lipid abnormalities in children and adolescents: a scientific statement from the American heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee, Council of Cardiovascular Disease in the Young, with the Council on Cardiovascular Nursing. *Circulation.* 2007;115:1948-1967. Epub 2007 Mar 21.

APPENDIX A
U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS AND RATINGS

The Task Force grades its recommendations according to one of 5 classifications (A, B, C, D, I) reflecting the strength of evidence and magnitude of net benefit (benefits minus harms):

A. The USPSTF strongly recommends that clinicians provide [the service] to eligible patients. *The USPSTF found good evidence that [the service] improves important health outcomes and concludes that benefits substantially outweigh harms.*

B. The USPSTF recommends that clinicians provide [the service] to eligible patients. *The USPSTF found at least fair evidence that [the service] improves important health outcomes and concludes that benefits outweigh harms.*

C. The USPSTF makes no recommendation for or against routine provision of [the service]. *The USPSTF found at least fair evidence that [the service] can improve health outcomes but concludes that the balance of benefits and harms is too close to justify a general recommendation.*

D. The USPSTF recommends against routinely providing [the service] to asymptomatic patients. *The USPSTF found at least fair evidence that [the service] is ineffective or that harms outweigh benefits.*

I. The USPSTF concludes that the evidence is insufficient to recommend for or against routinely providing [the service]. *Evidence that [the service] is effective is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.*

APPENDIX B

U.S. PREVENTIVE SERVICES TASK FORCE STRENGTH OF OVERALL EVIDENCE

The USPSTF grades the quality of the overall evidence for a service on a 3-point scale (good, fair, poor):

Good: Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes.

Fair: Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies, generalizability to routine practice, or indirect nature of the evidence on health outcomes.

Poor: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

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**Dr. Teutsch was recused from the discussion and voting on this issue.