Update on Screening, Etiology, and Treatment of Dyslipidemia in Children

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Context: Cardiovascular disease is a leading cause of morbidity and mortality. Early identification and treatment of risk factors that accelerate this condition are paramount to preventing disease. To this effect, the National Heart Lung and Blood Institute (NHLBI), endorsed by the American Academy of Pediatrics, issued updated pediatric guidelines for cardiovascular risk reduction in 2011. Integration of these guidelines into pediatric practice may lessen cardiovascular morbidity.

Evidence Acquisition: In addition to reviewing the NHLBI guidelines, a detailed literature search was performed on PubMed for clinical studies published between 2010 and 2013. Key search terms included “pediatric dyslipidemia/hyperlipidemia,” “cardiovascular disease,” “atherosclerosis,” “familial hypercholesterolemia,” “hypertriglyceridemia,” and “diabetes.” Additional citations from these publications were also reviewed. Final publications were selected for their relevance to the topic.

Evidence Synthesis: These guidelines contain several important recommendations relative to lipid management, including screening all children with nonfasting non-high-density lipoprotein-cholesterol (non-HDL-C) at ages 9–11 years, incorporation of aggressive lifestyle changes to meet cholesterol targets, and initiation of statin therapy for those with low-density lipoprotein-cholesterol (LDL-C) elevation. In addition, both type 1 and type 2 diabetes are now considered high-risk conditions and have stringent cholesterol targets. The primary aim is early identification of children with familial hypercholesterolemia; however, these recommendations have met with some controversy. The purpose of this update is to summarize these recent lipid guidelines, present the relevant controversies, highlight common cholesterol disorders, and discuss dyslipidemia specific to the pediatric diabetes population.

Conclusion: Identification and treatment of youth with dyslipidemia is of paramount importance to the reduction of future cardiovascular disease. Increasing the comprehension and application of the newest NHLBI guidelines is critical to improving cardiovascular outcomes. (J Clin Endocrinol Metab 99: 3093–3102, 2014)
of Pediatrics, issued integrated recommendations for cardiovascular (CV) risk reduction, including guidelines for management of hypertension, obesity, and hyperlipidemia (7). Specific rationale and grading of evidence can be reviewed in Ref. 8. Universal lipid screening should be performed with measurement of nonfasting non-HDL-C in all children ages 9–11 years and again 17–21 years of age. If abnormal, then repeat fasting lipid profile 2 weeks to 3 months apart. All values are expressed as milligrams per deciliter. To convert to SI units, divide total cholesterol, LDL-C, HDL-C, and non-HDL-C by 38.6; for TG, divide by 88.6.

Guidelines: 1. All children should have a nonfasting lipid profile measured between ages 9–11 years and again 17–21 years of age. 2. If abnormal, then repeat fasting lipid profile 2 weeks to 3 months apart. All values are expressed as milligrams per deciliter. To convert to SI units, divide total cholesterol, LDL-C, HDL-C, and non-HDL-C by 38.6; for TG, divide by 88.6. 3. Persistent elevation of a LDL-C level suggests a genetic etiology, and statin therapy is advised.

The guidelines offer comprehensive recommendations for evaluation and treatment of dyslipidemia, which start with lifestyle modification for 6 months. If LDL-C remains ≥130 mg/dL after lifestyle modifications in an individual with additional risk factors, medication may be considered (Table 3). Persistent elevation of a LDL-C level ≥190 mg/dL suggests a genetic etiology, and statin therapy is advised.

Guidelines for TG lowering are primarily geared toward diet and lifestyle changes. Pediatric treatment guidelines are focused on prevention of pancreatitis, and medication is currently indicated only for those with severe hypertriglyceridemia.

The aim of this update is to review the relevant discussions on evaluation and treatment of dyslipidemia in children, highlight cholesterol disorders that may be uncovered by the new screening guidelines, and review dyslipidemia in the pediatric diabetes population.

### Controversial Aspects of Screening Recommendations

Cholesterol screening recommendations in youth have been debated for decades, but these are the most aggressive recommendations to date. The screening guidelines are thorough by suggesting targeted screening for those at risk as well as universal screening at two different ages. The primary goal of universal screening is to identify those with familial hypercholesterolemia (FH), a condition without identifiable risk factors except family history. It has been shown that family history is incomplete in young individuals because parents and even grandparents may be too young to have demonstrated early CVD. One study showed that 1.2% of children with family history vs 1.7% of children without family history were diagnosed with familial hypercholesterolemia (FH) at a younger age (9). The second goal of universal screening is to use non-HDL-C to identify children with components of metabolic syndrome in an effort to highlight and prevent progression of additional components. These are two key pediatric populations that benefit from early recognition and management of cholesterol abnormalities.

There are several practical critiques. First, the guidelines do not adequately define the risk-to-benefit ratio, particularly regarding moderate dyslipidemia (10). Mild to moderate dyslipidemia may not persist into adulthood, and unnecessary therapy may have adverse effects. Although statin therapy has been proven safe and effective in adults, there is a paucity of long-term pediatric data on statin therapy. Statin trials have primarily included chil-

### Table 1. NHLBI Cholesterol Screening Guidelines and Cut Points (Adapted From Ref. 7)

<table>
<thead>
<tr>
<th>Acceptable</th>
<th>Borderlinea</th>
<th>Abnormalsa</th>
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<tbody>
<tr>
<td>Total cholesterol</td>
<td>&lt;170</td>
<td>170–199</td>
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<tr>
<td>LDL-C</td>
<td>&lt;110</td>
<td>110–129</td>
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<tr>
<td>Non-HDL-C</td>
<td>&lt;120</td>
<td>120–144</td>
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<tr>
<td>TGs</td>
<td></td>
<td></td>
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<tr>
<td>Ages 0–9 y</td>
<td>&lt;75</td>
<td>75–99</td>
</tr>
<tr>
<td>Ages 10–19 y</td>
<td>&lt;90</td>
<td>90–129</td>
</tr>
<tr>
<td>HDL-C</td>
<td>&gt;45</td>
<td>40–45</td>
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</tbody>
</table>

Guidelines: 1. All children should have a nonfasting lipid profile measured between ages 9–11 years and again 17–21 years of age. 2. If abnormal, then repeat fasting lipid profile 2 weeks to 3 months apart. All values are expressed as milligrams per deciliter. To convert to SI units, divide total cholesterol, LDL-C, HDL-C, and non-HDL-C by 38.6; for TG, divide by 88.6.

### Table 2. Risk Factors for CVD (Adapted From Ref. 7)

- **Family History**
  - Parent, grandparent, aunt, uncle, sibling with any of the following before age 55 y in a male or before age 65 y in a female: myocardial infarction, stroke, angina, coronary artery bypass, stent, angioplasty, sudden cardiac death
  - Parent with total cholesterol >240 mg/dL or known dyslipidemia

- **High-Risk Conditions**
  - T1DM and T2DM
  - Chronic renal disease/end-stage renal disease/post renal transplant
  - Post orthotopic heart transplant
  - Kawasaki disease with current aneurysms

- **Moderate-Risk Conditions**
  - Chronic inflammatory disease
  - Systemic lupus erythematosus
  - Juvenile inflammatory arthritis
  - Kawasaki disease—regressed coronary aneurysms
  - Nephrotic syndrome
  - HIV infection

- **High-Level Risk Factors**
  - Hypertension (blood pressure ≥99th percentile + 5 mm Hg) requiring medication
  - Cigarette smoker
  - BMI ≥97th percentile
  - Presence of high-risk condition(s)

- **Moderate-Level Risk Factors**
  - Hypertension not requiring medication
  - BMI ≥95th to <97th percentile
  - HDL <40 mg/dL
  - Presence of moderate-risk condition(s)
demonstrates that newly identified individuals gain 3.3 years of life. For every 100 people treated, 26 myocardial
infarcts were prevented, and there was an average lifetime
cost of $8700 per year gained (15, 16). The modifiable
outcome of metabolic syndrome is diabetes. One group
estimates that lifetime direct costs of type 2 diabetes mel-
litus (T2DM) in those diagnosed at ages 25–44 years are
between $124 000 and $130 000 (17). Therefore, eco-
nomic considerations are relevant, and we need additional
studies to properly project estimates of pediatric universal
screening, evaluation, and treatment.

Placebo-controlled studies to assess statin efficacy are
unlikely to be done at this stage, given known benefits, but
long-term, prospective studies of guideline implementa-
tion will be informative. The impact of diet and lifestyle
modification is unclear. Importantly, this should be iden-
tified as a teaching moment—an opportunity to educate
families as well as redirect anxiety that may come from
universal screening. Longitudinal studies demonstrate
that interventions in youth are effective in the prevention
of adult disease (3, 4, 18). For some, this provides tangible
evidence that even minimal lifestyle modifications may
delay or prevent devastating adult conditions.

### Other Considerations

Many youth are anticipated to have abnormal lipid levels
uncovered by this screening. Data from the National
Health and Nutrition Examination Survey suggest that
20–25% of children would qualify for retesting of their
cholesterol levels; an estimated 0.85% would be consid-
ered for statin medication (19). Obese children are more
likely than nonobese children (3.1 vs 0.6%) to need st-
atins, although this includes children who may respond to
lifestyle changes alone (20). Some question the validity of
placing this otherwise healthy population under such scru-
tiny. Conversely, there is a lack of consensus on how ag-
gressive to be, even in high-risk populations such as dia-
abetes (see Diabetes mellitus—a high-risk condition
below).

The concept of prescribing statins is daunting for most
pediatricians. Until now, training in dyslipidemia man-
agement has been limited because this has been considered
an adult disorder. The recommendations are written to
provide guidance, but children should be assessed practi-
cally and age appropriately. It may be reasonable to mon-
tor children with mild to moderate dyslipidemia who
have no other risk factors, with close attention to family
history and subsequent risk for developing additional as-
sociated conditions. The lipid guidelines are only one as-
pect of overall CV risk factor reduction; weight, blood

### Table 3. Criteria for Pharmacotherapy of Dyslipidemia
(Adapted From Ref. 7)—Use with Table 2

<table>
<thead>
<tr>
<th>Elevation in LDL-C</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>LDL-C ≥190 mg/dL</td>
<td><em>Lifestyle changes × 6 mo (may be abbreviated)</em></td>
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<tr>
<td></td>
<td>Consider statin therapy after age &gt;10 y or after Tanner 2 in boys, post menarche in girls</td>
</tr>
<tr>
<td>LDL-C ≥130–189 mg/dL with no family history or risk factors/Conditions</td>
<td><em>Lifestyle changes</em> Reassess every 6–12 mo</td>
</tr>
<tr>
<td>LDL-C ≥160–189 mg/dL with family history or 1 high-level risk factor/condition or ≥2 moderate-level risk factors/conditions</td>
<td><em>Lifestyle changes × 6–12 mo</em> Consider statin therapy after age &gt;10 y or after Tanner 2 in boys, post menarche in girls</td>
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<tr>
<th>Elevation in TGs</th>
<th>Criteria</th>
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| TGs ≥500 mg/dL     | *Lifestyle changes* 
|                    | Counsel on risk of pancreatitis |
|                    | Referral to lipid specialist |
| TG >200–499 mg/dL  | *Lifestyle changes* 6–12 mo 
|                    | Consider omega-3 fish oil therapy |
|                    | Consider referral to lipid specialist, especially if LDL-C target achieved |
| TG ≥100–200 mg/dL (≤10 y) or ≥130–200 mg/dL (≥10 y) | *Lifestyle changes* 6–12 mo 
|                    | Increase dietary fish content |
|                    | Fasting lipid panel every 6 mo |
| TG <100 mg/dL (≤10 y) or <130 mg/dL (≥10 y) | *Continue lifestyle changes* 
|                    | Fasting lipid panel annually |

*Lifestyle changes: diet and physical activity. Diet: CHILD-1 diet for 3–6 months. If no improvement in lipids, then CHILD-2 Diet. Physical activity: vigorous activity 60 min/day and screen time (television, texting, computer, etc) limited to less than 2 hours per day.*
pressure, physical activity, and other factors are also critical to CVD risk, and the NHLBI guidelines address these issues as well.

**Etiology of Hyperlipidemia**

This section briefly reviews common and important primary disorders of cholesterol metabolism. A full review of dyslipidemia can be found separately (21). Correction of secondary causes (Table 4) should normalize lipid levels, if not compounded by underlying genetic factors.

**Familial hypercholesterolemia**

A child with significant and isolated elevation of LDL-C ≥160 mg/dL should be considered to have FH, particularly if there is a family history of early CVD. This is an important diagnosis because risk of premature coronary artery disease is substantially elevated compared to the general population. The National Lipid Association has published recommendations for the diagnosis and management of this condition (22).

FH often have CV events such as myocardial infarction, stroke, and renal artery stenosis before age 50. Heterozygous FH (HoFH), evidenced by extremely elevated LDL-C levels, is associated with rapidly progressive atherosclerosis, CV events, and mortality in the first two decades of life. Heterozygous FH affects approximately 1 in 500 individuals in the United States, whereas HoFH occurs in 1 in 10⁶.

Early detection is critical for early intervention; diagnosis of FH is possible in early childhood but will be unrecognized if LDL-C is not measured, especially in patients whose parents are unaware of their own diagnosis due to young age or lack of assessment. It is worrisome that some may escape diagnosis until the time of a CV event (25).

A clinical diagnosis of FH can be made when there are more than two first-degree relatives with characteristic LDL-C levels (with or without premature CVD) or by the presence of tendon xanthomas. Notably, xanthomas are rarely seen in children and adolescents. After diagnosis, cascade screening should occur in all first-degree relatives after age 2 years, and appropriate treatment should be pursued.

As a condition of early atherosclerosis, lipid goals include LDL-C ≤130 mg/dL, or lower if there are additional CVD risk factors (22). Treatment of heterozygous FH before puberty is focused on lifestyle changes. After puberty, treatment with statins may be indicated. Crucially, individuals with HoFH should be evaluated by a lipid specialist and statins started earlier due to a substantially earlier risk of coronary artery disease. LDL apheresis and/or liver transplant have been the historical treatments in this subset, although efficacy and success are variable. Novel medical therapies for adults with HoFH have recently been approved in the United States (26, 27).

**Hypertriglyceridemia**

*Mild to moderate hypertriglyceridemia (TG 150–500 mg/dL)*

Identification of hypertriglyceridemia is common, particularly in youth with diabetes, overweight, and obesity. Secondary causes of TG elevation such as hypothyroidism, polycystic ovarian syndrome, and medication effects (eg, oral contraceptives and isotretinoin) should be assessed. Treatment or amelioration of secondary causes is generally effective in normalizing TG levels when not compounded by inherited disorders. In the setting of obesity, TG management is primarily aimed at weight control. Reduced caloric intake and increased exercise are associated with a significant reduction and stabilization of TG as well as elevation of HDL-C (28).
Severe hypertriglyceridemia (TG > 500 mg/dL)

Severe hypertriglyceridemia is less common. Of 300 hypertriglyceridemia patients followed at one pediatric preventive cardiology clinic, 7% had TG above 400 mg/dL, and 2% above 1000 mg/dL (29). Patients with severe hypertriglyceridemia are more likely to have a defect in lipoprotein lipase (LPL). Inherited defects in the LPL gene, in its associated apolipoproteins (ApoC2, Apo E, ApoC5), or in GH1HP1, an endothelial binding site for LPL, have all been shown to cause defective LPL activity (30, 31). In these conditions, TG may rise up to 10 000 mg/dL. Complete defects are extremely rare and typically present early in life. Partial defects of LPL are also uncommon but may be unmasked by a secondary cause.

Therapy is aimed at prevention of pancreatitis, which is associated with severe hypertriglyceridemia and postprandial TG excursions. Patients with TG ≥500 mg/dL should be prudently counseled on the symptoms of pancreatitis (nausea, vomiting, and abdominal pain, especially after a high-fat meal). Treatment is generally focused on limiting fat intake. Unfortunately, even extreme fat-restricted diets may not be effective prevention.

Familial combined hyperlipidemia (FCHL)

FCHL is characterized by a mixed dyslipidemia, (high risk of) premature CVD, and a vertical transmission profile (32). The LDL-C and TG may be high or normal, HDL-C can be normal or reduced, and there is significant production of small, dense LDL particles. Contrary to FH, FCHL is less likely to be diagnosed in children because LDL-C elevations may not occur until after adolescence.

At a prevalence of 1–2%, particularly among those with early CVD, this is one of the most common inherited dyslipidemia syndromes (32). Uniquely, there may be significant heterogeneity even within a single family. The pathophysiological hallmark of FCHL is overproduction of very low-density lipoprotein (VLDL)-cholesterol. Circulating ApoB levels may rise before cholesterol levels, so in those with a family history of early CV events, measurement of ApoB levels may be a better marker for this condition.

In adults, FCHL is often associated with features of metabolic syndrome. Given the common association of insulin resistance and VLDL overproduction in both disorders, some suggest that FCHL is a continuum that progresses into metabolic syndrome and then T2DM (33). Several genetic loci have been associated with ApoB regulation and T2DM, including upstream stimulating factor 1, transcription factor 7-like 2, and hepatocyte nuclear factor 4-α (34, 35). Most groups agree that the FCHL phenotype is likely polygenic, or at least pleiotropic.

Treatment is related to lifestyle changes and obesity management to reduce comorbidities. If FCHL, metabolic syndrome, and T2DM are on the same spectrum, then early diagnosis and treatment are critical.

Treatment of Dyslipidemia

Lifestyle changes

Lifestyle changes are the core of dyslipidemia treatment. This includes physical activity 60 minutes a day, screen time ≤2 hours a day, attainment of ideal body weight (body mass index [BMI] ≤85th percentile for age and gender), and optimization of blood pressure. Dietary therapy is initiated with the Cardiovascular Health Integrated Lifestyle Diet-1 (CHILD-1) for 3–6 months, which includes total fat less than 30% of daily caloric intake, saturated fat 8–10%, avoidance of trans fats, and cholesterol intake less than 300 mg/d. This may be advanced to a CHILD-2 diet specific to LDL or TG elevation, which includes further restriction of saturated fat less than 7% and cholesterol intake less than 200 mg/d. This safe and effective diet is associated with normal growth and development in children as early as 6–7 months of age (7).

For LDL-C reduction, water-soluble fiber and plant sterols may complement the CHILD-2 diet. Intake of psyllium 6 g/d for children 2–12 years old and 12 g/d for those above 12 years can modestly lower LDL-C levels by approximately 7% (36). Plant sterols and plant stanol esters compete with cholesterol for intestinal absorption via Niemann-Pick C1-like protein. Plant sterols can be taken as supplements or found in specially formulated foods. Doses of up to 2 g/d have been demonstrated to reduce LDL-C by 10–15%. Intake of 2–3 g/d may slightly reduce α- and β-carotene absorption, but a daily multivitamin or increased fruit and vegetable intake will prevent this. Absorption of vitamins D and A has not been affected.

Individuals with elevation in TG should follow the CHILD-2 TG diet with a focus on sugar reduction; plant sterols are not indicated. Simple sugars should be replaced with complex carbohydrates, sugar-sweetened beverages should be eliminated, and consumption of fish should be encouraged to increase omega-3 fatty acid intake. For obese children, nutrition therapy should include calorie restriction and age-appropriate increased physical activity.

For those with severe hypertriglyceridemia, intake is restricted to an ultra-low-fat diet containing less than 10% total fat. This should be implemented and followed under the guidance of a pediatric nutrition expert to ensure adequate essential fatty acid and caloric intake. Unfortu-
nately, even extreme fat restriction may not provide effective prevention.

**Pharmacological treatment of hypercholesterolemia**

If lifestyle changes over 6–12 months are inadequate to achieve target LDL-C levels, medication may be indicated in children above the age of 10 years (Table 3). Guidelines for pharmacotherapy of pediatric dyslipidemia were published in 2007 (7, 37). Consultation with a lipid specialist may be considered.

Statin therapy in children with FH has been shown to reduce LDL-C by 20–40% (38, 39). Although limited in number, enrollment, and duration, statins have been demonstrated to be safe, well-tolerated, and efficacious in children. Statins that are Food and Drug Administration (FDA)-approved in children include pravastatin, simvastatin, lovastatin, atorvastatin, and fluvastatin. Although adult guidelines do not recommend routine screening of liver and muscle enzymes while on statin therapy, pediatric guidelines have not followed suit. Adult guidelines are based on study populations that rarely include children, so conservative approaches in pediatrics may be appropriate. In youth, statins should be started at the lowest dose with baseline measurements of alanine aminotransferase, aspartate aminotransferase, and creatinine kinase performed. These levels plus a fasting lipid profile should be repeated 4 and 8 weeks after initiation of therapy, and then every 3–6 months (37). If liver enzymes are above three times the upper limit of normal, if creatinine kinase is above 10 times the upper limit of normal, or if the patient reports any adverse effects, medication should be stopped to determine whether there is improvement. Importantly, statins may be teratogenic, so females should be counseled and prescribed contraceptive therapy when indicated.

Target LDL-C is typically below 130 mg/dL, but it is ideally under 100 mg/dL in high-risk populations such as FH patients. If target levels are not achieved within 3 months, the dose can be incrementally increased to maximum dose. Occasionally, a second agent such as a bile acid sequestrant may be useful (40). Multiple drug therapy should be guided by a lipid specialist.

**Pharmacological treatment of hypertriglyceridemia**

Treatment of hypertriglyceridemia is primarily driven toward lifestyle changes delineated above. Historically, the influence of hypertriglyceridemia on atherosclerotic lesions has been less clear. Only recently has there been evidence that TG elevations may predispose to atherosclerosis and CVD independent of metabolic risks (41–43).

For severe hypertriglyceridemia, pharmacological therapy is limited and treatment should be guided by a lipid specialist. Although omega-3 fatty acids in the form of docosahexaenoic acid and eicosapentaenoic acid at 2–4 g daily have been shown in adults to lower TG by 20–30% (44), prescription forms of omega-3 fatty acids are not currently FDA-approved for children. Fibrates and niacin lower TG levels via modulations of LPL and thus may be largely ineffective in those with defective LPL activity. Orlistat, a pancreatic lipase inhibitor, was combined with a very low-fat diet in two siblings with compound heterozygous mutations in LPL. Three years of treatment led to a reduction of fasting TG below 600 mg/dL, and recurrent pancreatitis had all but resolved (45).

Novel treatment for inherited defects of LPL via gene therapy has been approved in Europe. Alipogene tiparvovec contains a gain-of-function LPL variant, and short-term trials show improved postprandial chylomicron metabolism and metabolic parameters (46).

**Diabetes Mellitus—A High-Risk Condition**

Previously, type 1 diabetes mellitus (T1DM) was labeled a high-risk condition for CVD, whereas T2DM conferred a moderate risk. Now, T1DM and T2DM are both accorded the highest possible risk classification and are considered a CVD equivalent (7, 47).

Diabetes is associated with more severe and earlier onset of CVD, compared to the general population. Despite clinical and etiological distinction, both forms are associated with vascular damage and accelerated atherosclerosis. Long-term studies of complications in early onset diabetes remain limited in scope, but outcome is particularly worrisome because the incidence of diabetes is increasing and macrovascular complications correlate with duration of diabetes as well as glycemic control.

**Type 1 diabetes mellitus**

The leading cause of death in adults with T1DM is coronary artery disease, despite similar or less atherogenic profiles when compared to age-, sex-, and BMI-matched controls (48, 49). This is one of the rare important instances, like HoFH, when CVD presents in childhood. Although the etiology remains enigmatic, glycemic control, hypertension, nephropathy, and dyslipidemia at least contribute to this process.

Relative insulin deficiency increases hepatic release of VLDL and subsequent elevation in TG and LDL. Therefore, prevention of dyslipidemia is partly related to glycemic control; long-term studies have shown that improved glucose control is beneficial (50, 51). However, intensive glucose management has its drawbacks, including weight gain and hypoglycemia, as evident in adult studies (52).
Individuals with T1DM are more likely to be overweight (53). Metabolic risk factors may be lower in the T1DM group than in matched overweight nondiabetics (54, 55); however, as insulin sensitivity decreases, adolescents with T1D develop more atherogenic risk factors, whereas those with the highest markers of insulin sensitivity have a risk profile comparable to the nondiabetic adolescent (56).

Endothelial dysfunction in diabetes mellitus appears to be present as early as preadolescence, and pulse wave velocity as a measure of arterial stiffness has been shown to worsen with an increase in LDL-C, adiposity, and glycemic control (57). Optimization of these parameters may improve outcomes; therefore, reduction of LDL-C is another focus of therapy.

Total cholesterol and non-HDL-C are higher in children with T1DM than the general population (58). One group identified 31% of its T1DM population as having LDL-C levels $\geq 100$ mg/dL (53). Interestingly, a recent study showed that cholesterol synthesis in T1DM is not elevated compared to nondiabetic subjects (59), suggesting that enhanced cholesterol absorption may be a significant but modifiable contributor to dyslipidemia in T1DM. If substantiated, the role of cholesterol absorption inhibitors may become more prominent. One small study showed an additional 15–16% reduction in both LDL-C and non-HDL-C levels in T1DM patients who had cholesterol absorption inhibitors added to statin therapy (60).

Levels of HDL-C have been shown paradoxically elevated in T1DM compared to the general population. There is much speculation about the mechanism and relevance of this, but prospective studies have not consistently identified this as a significant cause for CVD events (61).

**Type 2 diabetes mellitus**

The increased prevalence of obesity in youth has led to an increase in T2DM in adolescents. Duration of disease and glycemic control are important factors in the development of long-term complications. Despite increasing incidence of T2DM in youth, many targeted medications are not approved in adolescents, and there are little data to guide treatment strategies. The treatment options for the Type 2 Diabetes in Adolescents and Youth (TODAY) study group were created with this goal in mind. Recently, 3-year data became available and showed disheartening results. Loss of glycemic control (defined as hemoglobin A1c $\geq 8\%$) occurred in 52, 39, and 47% of participants assigned metformin, metformin + rosiglitazone, and metformin + lifestyle intervention, respectively (62). Data regarding lipid outcome were also disappointing. Dyslipidemia was present at baseline and worsened over 36 months. Prevalence of elevated LDL-C ($\geq 130$ mg/dL) and treatment for hyperlipidemia increased from 4.5 to 10.7%, with fewer individuals maintaining LDL-C below 100 mg/dL. Only 10 of the 46 statin-treated patients achieved the target LDL-C level. Prevalence of TG abnormalities rose from 21 to 23% (63). Of note, highly atherogenic, small, dense LDL particles did decline somewhat.

Studies in adults with diabetes demonstrate that optimal statin therapy lowers LDL-C and improves CV risk. In fact, the American Heart Association revised adult guidelines in 2013 and controversially eliminated specific LDL-C targets, instead recommending high-dose statin therapy in all diabetes patients over age 40 years, and earlier for those with evidence of CVD (64). Pediatric recommendations do not reflect this very recent change yet. However, the inability to improve dyslipidemia in youth over the short term in a randomized, controlled study bodes poorly for the future.

**Management of dyslipidemia in diabetes**

Despite the association with CVD, many adults and children with diabetes have been shown to have suboptimal lipid management (53, 65). The target LDL-C is below 130 mg/dL, ideally below 100 mg/dL. Aggressive management strategies are advocated in pursuit of this goal. Like the NHLBI, the American Diabetes Association (ADA) guidelines for pediatrics do not distinguish between T1DM and T2DM. A fasting lipid panel should be obtained at age $\geq 10$ years (at puberty) in those without family history of hypercholesterolemia or early CVD; in those with family history or known CV risk factors, lipid screening should be performed once glycemic control has been achieved in all children after the age of 2 years (66). From here, the ADA guidelines diverge slightly from the NHLBI in this high-risk population. The ADA guidelines state that if LDL-C is greater than 130 mg/dL with one or more CV risk factors or LDL-C is above 160 mg/dL with no risk factors, efforts should focus on optimal glycemic control and overall lifestyle changes; lipid panel should be repeated annually (66). Adjunctively, other comorbidities of diabetes should be addressed. If target LDL-C levels are not met, then statin therapy may be indicated after the age of 10 years. This divergence leaves LDL-C levels between 130 and 160 mg/dL open to interpretation. Many are following the more aggressive NHLBI guidelines in this youthful, high-risk population. It may be reasonable to monitor these patients closely if glycemic control is optimal and there are no other risk factors. It may also be sensible to delay statin therapy if there is an opportunity to optimize glycemic control and comorbidities. However, relatives may be too young to have a known history of early CVD, so detailed family history should be revisited.
at every opportunity. Updated guidelines for CV risk reduction specific to children with T1DM were in press at the time of this publication, so it is hopeful that this divergence will be addressed.

Only one completed pediatric statin trial in T1DM was identified. In a population with low-risk LDL-C, atorvastatin led to modest reductions in LDL-C and possible benefits of reduced arterial stiffness (67). Another group initiated a trial of statin plus cholesterol absorption inhibitor in children and adolescents, but of 109 eligible candidates, only nine were actually enrolled (68). Large, prospective study data may be forthcoming, including information from an international multicenter study of statin and antithypertensive therapies, as well as from a T1DM registry in the United States (69, 70). It is anticipated that these large studies may provide additional evidence for recommendations in this field of tremendous uncertainty. Clearly, there is a distinct need for additional studies in youth with diabetes to assess efficacy of therapy as well as impact on coronary end points.

Conclusions
Early recognition and treatment of dyslipidemia in children may lead to modification of risk factors that contribute to adult CVD. Aggressive management should continue to focus on youth with high-risk conditions associated with accelerated atherosclerosis, but prevention of additional risk factors is also key. As we address lipid abnormalities in youth, outcome data must be tracked meticulously so that guidelines may be revised accordingly to optimize the risk-to-benefit ratio. Prevention of disease states such as T2DM is just as critical as early identification of genetic disorders in improving quality of life as well as reducing CV morbidity.

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