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CHILDREN/ADOLESCENTS/YOUNG ADULTS AND ATHEROSCLEROSIS (D.P. WILSON, SECTION EDITOR)

Are Clinicians Aggressive Enough in Treating Diabetes-Related Hyperlipidemia in Youth?

Sarah Jackson[1] · **Ana Creo**[1] · **Seema Kumar**[1]

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Abstract

Purpose of Review Cardiovascular disease is the leading cause of death in patients with type 1 diabetes (T1D) and type 2 diabetes (T2D). Subclinical atherosclerotic changes are noted in youth with diabetes; therefore, timely identification and management of modifiable cardiovascular risk factors including hyperlipidemia is crucial. We review the current guidelines for hyperlipidemia screening and treatment in youth with T1D and T2D. We discuss the efficacy of non-pharmacological strategies including dietary modifications, exercise, and glycemic control and pharmacological therapy. We summarize reported rates of treatment of diabetes-related hyperlipidemia in youth.

Recent Findings Hyperlipidemia is prevalent among youth with T1D and T2D. Vast majority of youth with diabetes-related hyperlipidemia do not receive lipid-lowering treatments. There are several factors that contribute to suboptimal management of hyperlipidemia in youth with diabetes including limited data on efficacy and safety of statins in youth with diabetes.

Summary We propose strategies to improve hyperlipidemia management including education of providers and patients, quality improvement methods, and electronic health record alerts. Additionally, further studies are warranted to examine the safety of statins in youth with diabetes, cost–benefit analysis to aggressive screening and treatment, and long-term effect for improving cardiovascular morbidity and mortality.

Keywords Type 1 diabetes mellitus · Type 2 diabetes mellitus · Hyperlipidemia · Statins

Introduction

Type 1 diabetes (T1D) and type 2 diabetes (T2D) are associated with increased risk for morbidity and premature mortality from cardiovascular disease (CVD) [1–6]. CVD is the leading cause of death in patients with diabetes [3–5, 7]. This is particularly important given the rising prevalence of T1D and T2D among children [8, 9]. The prevalence of T2D in youth appears to be increasing at a more rapid pace than that of T1D likely due to the increasing rates of obesity in children and adolescents particularly among American Indian, Asian or Pacific Islander, Black, and Hispanic youth [9]. While diabetes itself is an independent risk factor for CVD, many youth with diabetes have co-existing CVD risk factors which further increase CVD risk [10–12]. Lastly, the prevalence of having multiple CVD risk factors is increasing over time, especially amongst non-white youth and those with T2D [13].

While macrovascular complications occur typically during adult life, subclinical changes in the vessels that precede clinical cardiovascular events, such as increased carotid intima media thickness and arterial stiffness, have been demonstrated in youth with T1D [14] and T2D [15]. These changes are more prevalent and pronounced in those with T2D compared to those with T1D [16, 17]. Hyperlipidemia is a modifiable risk factor for developing CVD in youth with both T1D and T2D [11, 18–22]. Unfortunately, only a small fraction of youth with diabetes who have hyperlipidemia receive appropriate lipid-lowering treatment [18, 19, 23]. The low rates of treatment stem partly from scarce data on risks and benefits of statin use in youth with diabetes and

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✉ Seema Kumar
kumar.seema@mayo.edu

[1] Division of Pediatric Endocrinology, Department of Pediatric and Adolescent Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN, USA

lack of familiarity of many pediatric care providers with statins [24, 25]. Here, we examine the prevalence of hyperlipidemia in youth with diabetes and discuss current guidelines for screening and management of hyperlipidemia in this population. We review the overall low rates of lipid-lowering treatment in youth with diabetes and discuss opportunities to promote optimal lipid management for future cardiovascular health.

Prevalence of Hyperlipidemia in Youth with Diabetes

Hyperlipidemia is more prevalent in youth with diabetes compared to those without diabetes. Among 682 youth 21 years old or younger with T1D (mean, 12.6 ± 4.3 years), 15.4% had a total cholesterol (TC) above 200 mg/dL in comparison to 11.2% of subjects age 4 to 21 years old in the National Health and Nutrition Examination Survey 2001–2002 [21].

Type 1 Diabetes

Hyperlipidemia is prevalent in youth with T1D worldwide (Table 1). In the SEARCH for Diabetes in Youth study, a cross-sectional, population-based study, conducted in six centers from the USA, about half (48%) of youth with T1D ($n = 2113$) were noted to have low-density lipoprotein cholesterol (LDL-C) levels above 100 mg/dL and 15% had LDL-C levels ≥ 130 mg/dL [18]. Approximately 3% of those 10 years of age and older had LDL-C level ≥ 160 mg/dL, a level at which medications would be indicated despite dietary and lifestyle modifications. However, only 1% of the youth with T1D received lipid-lowering medication therapy suggesting under-treatment of lipid abnormalities in those with T1D. Among those that were 10 years of age and older, hypertriglyceridemia defined as triglycerides (TG) > 150 mg/dL was seen in 10%, and high-density lipoprotein cholesterol (HDL-C) < 40 mg/dL in 12%. Another study by Maahs et al. in 360 youth with T1D demonstrated a TC ≥ 200 mg/dL in 17%, non-HDL-C ≥ 130 mg/dL in 28%, ≥ 160 mg/dL in 11%, and ≥ 190 mg/dL in 3% [23]. Despite the high rates of dyslipidemia, lipid-lowering medications were prescribed in only 6% of patients [23]. In the German prospective documentation and quality management system (DPV) study that included 27,358 children and adults with T1D consecutively registered at 195 German and Austrian centers, dyslipidemia (defined as at least one abnormal lipid parameter, TC > 200 mg/dL, LDL-C > 130 mg/dL, or HDL-C < 35 mg/dL) was noted in 28.6% of patients overall [19]. LDL-C > 130 mg/dL was seen in 11% and LDL-C above 160 mg/dL in 5.3% of patients. However, only 0.4% of patients received lipid-lowering therapy. In a population based study of youth with T1D in Norway, LDL-C was > 100 mg/dL in 34.5% [10]. In a study of 229 children and adolescents with T1D in the UK, 38% had LDL-C > 100 mg/dL and 10.8% had LDL-C > 130 mg/dL, the thresholds for lifestyle and drug intervention respectively [26]. A high prevalence of dyslipidemia has also been noted in Brazilian youth with T1D [27].

Increasingly hyperlipidemia associated with increased duration of diabetes has been described in patients with T1D from Norway [10], Netherlands [28], and USA [29]. In a longitudinal study from the Netherlands of 3728 youth younger than 19 years with T1D and 18,513 non-diabetic controls, the prevalence of hypercholesterolemia (clinical diagnosis or LDL-C ≥ 100 mg/dL and/or TC ≥ 200 mg/dL, or the use of lipid-lowering medication), 20 years following the onset of diabetes was 66.7% in those with T1D versus 7.1% in nondiabetic controls [28]. Ninety-eight percent of youth with T1D and hypercholesterolemia were not treated pharmacologically for a duration at least 1 year during follow-up and 53% were untreated with medications for a period ranging between 2 and 5 years. In a retrospective chart review, by Kim et al., of an ethnically diverse population of patients between the ages of 10 and 22 years with T1D ($n = 1701$, 23% Hispanic and 17% non-Hispanic Black) at a single center between 2015 and 2017, 33% had an LDL-C above the recommended goal of 100 mg/dL and 9% had LDL-C ≥ 130 mg/dL [29]. Increased age, diabetes duration, higher HbA1c, female sex, Hispanic ethnicity, and obesity were associated with higher LDL-C.

In summary, hyperlipidemia is prevalent among youth with T1D with one third to half of youth in various studies having LDL-C above the optimal level of 100 mg/dL. The vast majority of youth with hyperlipidemia do not receive lipid-lowering treatment.

Type 2 Diabetes

In the SEARCH for Diabetes in Youth study, among 278 youth 10 years of age and older with T2D (63% female, 29% African American, 27% American Indian, 20% non-Hispanic White, and 17% Hispanic), LDL-C was more than the optimal level of 100 mg/dL in more than half (57%) and a quarter (24%) had LDL-C ≥ 130 mg/dL [18] (Table 1). Approximately 9% had LDL-C ≥ 160 mg/dL, a level that would warrant medication if the level was persistent despite diet and lifestyle modifications (Table 1). However, only 5% were receiving lipid-lowering medications. Hypertriglyceridemia was seen in 29% and 44% had HDL-C < 40 mg/dL. In another study of 298 youth with T2D with a higher proportion of Hispanic youth (58% Hispanic), similar rates of hyperlipidemia were reported (48% with LDL-C > 100 mg/dL and 16% with LDL-C > 130 mg/dL) [29].

Table 1 Studies reporting rates of lipid-lowering treatments in youth with type 1 diabetes mellitus and type 2 diabetes mellitus

Study/study type	Subjects	Hyperlipidemia/lipid-lowering treatment
Kershner et al Journal of Pediatrics, 2006[18] Cross sectional population-based study	2165 subjects (age < 19 years at diagnosis of diabetes) with T1D and 283 with T2D enrolled in SEARCH for Diabetes in Youth study from 6 centers in USA	Overall, 12% had LDL-C ≥ 130 mg/dL and 3% had LDL-C ≥ 160 mg/dL Among youth ≥ 10 years of age, 24% with T2D and 15% with T1D had LDL-C ≥ 130 mg/dL and 9% with T2D and 3% with T1D had LDL-C ≥ 160 mg/dL. Only 1% were receiving lipid-lowering medication
Schwab et al Diabetes Care, 2006[19] Cross sectional study	27,358 consecutively registered children and adults with T1D (age 0.25 to 26 years) in German and Austrian centers	LDL-C > 130 mg/dL in 11% and LDL-C > 160 mg/dL in 5.3%. Only 0.4% of patients received lipid-lowering medications
Maahs et al Journal of Pediatrics, 2007[23] Retrospective longitudinal study	360 participants (2–21 years of age) with T1D from single pediatric diabetes center in USA	Non-HDL-C ≥ 160 mg/dL in 10.6% and ≥ 190 mg/dL in 3.3%. 6.4% of patients were started on lipid-lowering medications
Margeirsdottir et al. Diabetologia 2008[10] Population based study	1658 subjects with T1D from 26 pediatric clinics in Norway Mean age 13.1 years (range 1.1–23.2 years)	10% had LDL-C > 130 mg/dL and at least once cardiovascular risk factor. 2% had LDL-C > 160 mg/dL. 3% of those who should have been were receiving lipid-lowering treatment (statins) in line with ADA guidelines
TODAY Study Group Diabetes Care 2013[32] Longitudinal study	699 youth with T2D from the TODAY clinical trial. Age at 14 ± 2 years Lipids measured over 36 months or until loss of glycemic control	Prevalence of LDL-C ≥ 130 mg/dL or taking LDL-C-lowering medication increased over the 36-month period, going from 4.5 to 10.7%. 46 participants were placed on statin therapy, but only 10 of them achieved an LDL-C goal of < 100 mg/dL
Ahmadizar et al British Journal of Clinical Pharmacology 2018[28] Retrospective cohort study	3728 children (< 19 years of age) with T1D and 5 age and gender matched diabetes-free controls from Clinical Practice Research Datalink, England and Wales	66.7% of T1D had hypercholesterolemia vs 7.14% of controls 20 years after onset of diabetes 53% with hypercholesterolemia were untreated for 2–5 years
Kim et al International Journal of Pediatric Endocrinology 2020[29] Retrospective chart review	1701 subjects with T1D and 298 with T2D between ages 10 and 22 that were not on statins	9% of subjects with T1D had LDL-C ≥ 130 mg/dL 16.9% of those with T2D had LDL-C ≥ 130 mg/dL
Greenup et al Endocrinology, Diabetes and Metabolism, 2021[30] Retrospective longitudinal study	42 children with T2D diagnosed at ≤ 10 years of age at a single pediatric center in USA	Of the 27 that had baseline lipids, 25.9% had LDL-C ≥ 130 mg/dL At the 2–3-year follow-up: 11.8% had LDL-C ≥ 130 mg/dL and only 5.9% were on lipid-lowering medications At the 4–5-year follow-up, LDL-C was ≥ 130 mg/dL in 28.5% and only 7.1% were on lipid-lowering medications

T1D, type1 diabetes mellitus; *T2D*, type 2 diabetes mellitus; *LDL-C*, low-density lipoprotein cholesterol; *non-HDL-C*, non-high-density lipoprotein cholesterol

Hyperlipidemia is also prevalent in youth younger than 10 years with T2D and rates of lipid-lowering treatments are low in that age group. In a single center study of children with T2D that were diagnosed at age 10 years or under, LDL-C ≥ 130 mg/dL was noted in 25.9% of patients at baseline and in 11.8% at the 2–3-year follow-up. However only 5.9% were on a lipid-lowering medication at the 2–3-year follow-up [30]. High prevalence of hyperlipidemia has been reported in youth with T2D from India [31].

Similar to the data in youth with T1D, lipid abnormalities progress over time in youth with T2D. In the SEARCH for Diabetes in Youth study, of the 699 youth with recent onset T2D enrolled in the TODAY study (Treatment Options for Type 2 Diabetes in Adolescents and Youth Phase II Study), number of participants with LDL-C ≥ 130 mg/dL or using lipid-lowering therapy increased from 4.5 to 10.7% over 36 months and only 55.9% remained at LDL-C goal (< 100 mg/dL) over that time [32]. Of the 46 that had been treated with statins, 32 had at least one follow-up measurement and only 10 achieved target LDL-C goal.

In summary, hyperlipidemia is seen in up to half of youth with T2D and increases with the duration of diabetes. However, only a very small proportion receive lipid-lowering medications despite the presence of additional CVD risk factors including obesity and hypertension.

Association of Hyperlipidemia in Youth with Atherosclerosis and Cardiovascular Disease

Subclinical atherosclerosis begins during childhood and young adult life. Serum concentrations of TC, LDL-C, and HDL-C are associated with subclinical signs of atherosclerosis (fatty streaks and fibrous plaques) in children and young adults [33, 34]. Children with T1D have evidence for early atherosclerosis with increased arterial stiffness and aortic intima media thickness compared with controls [35–37]. In a study of 1376 youth with T1D and 157 with T2D from the SEARCH study, elevated arterial stiffness was found in 8% of those with T1D and 49% of T2D participants [35]. Each standard deviation increase in LDL-C was associated with 1.28 increased odds of elevated arterial stiffness in youth with T1D. This association was similar but not statistically significant in T2D. The association between LDL-C and arterial stiffness in T1D was not significant after adjustment for waist-to-height ratio or insulin sensitivity score, thereby suggesting that obesity and insulin resistance partially account for the adverse effects of LDL-C on cardiovascular health in youth with T1D.

Screening Guidelines for Youth with Diabetes

The American Diabetes Association (ADA) recommends that initial lipid screening be performed in youth with T1D when initial glycemic control has been achieved and age is ≥ 2 years (Table 2) [38]. If initial LDL-C is below 100 mg/dL, subsequent testing is recommended at 9–11 years of age. Initial testing may be done with a calculated non-HDL-C level using a non-fasting sample with confirmatory testing with a fasting lipid panel. If the lipid screen between 9 and 11 years of age is normal, lipids should again be measured within 3 years as glycemic control and other cardiovascular risk factors can change during adolescence [38]. Annual monitoring is recommended if the results are abnormal. The International Society for Pediatric and Adolescent Diabetes (ISPAD) recommends screening for dyslipidemia soon after diagnosis (when diabetes has stabilized) in all children with T1D from age ≥ 11 years [39]. Screening as early as age 2 is recommended in those with the family history of

Table 2 Screening recommendations for hyperlipidemia in youth with diabetes

American Diabetes Association	Type 1 diabetes	Type 2 diabetes
Initial	Glycemic control established and age ≥ 2 years	At the time of diagnosis when glycemic control established
Subsequent	-If LDL-C < 100 mg/dL repeat between 9 and 11 years of age, then every 3 years if normal - Annual lipid panel if abnormal results	If initial screen is normal, obtain lipid panel annually
International Society for Pediatric and Adolescent Diabetes	Type 1 diabetes	Type 2 diabetes
Initial	If ≥ 11 years screen after diagnosis If family history and other risk factors present, screen as early as 2 years of age	Once glycemic control established
Subsequent	Every 5 years if normal	Annually if normal if abnormal repeat in 6 months

LDL-C, low-density lipoprotein cholesterol [38]

hypercholesterolemia or early CVD or if the family history is unknown. Repeat screening is recommended every 5 years if the results are normal.

For youth with T2D, the ADA and ISPAD recommend that lipid testing be performed at diagnosis when initial glycemic control has been achieved and annually thereafter if the initial screen is normal [38, 40].

Treatment of Hyperlipidemia in Youth with T1D and T2D

The optimal goals recommended by the ADA and by ISPAD for youth with diabetes (T1D and T2D) are LDL-C < 100 mg/dL, HDL-C > 35 mg/dL, and TG < 150 mg/dL [38–40] (Table 3).

The requirement for fasting may impede testing as fasting could be inconvenient particularly for children with diabetes and increases the likelihood of hypoglycemia. The recommendations for fasting for measurement of lipids should be reconsidered as lipids and lipoproteins do not change significantly following normal food intake. Four large prospective studies demonstrated maximal mean changes of + 26 mg/dL for TG, − 8 mg/dL for TC, − 8 mg/dL for LDL-C, and − 4 mg/dL for HDL-C [43].

Improvement in Glycemic Control

Suboptimal glycemic control in youth with diabetes is associated with higher TC, LDL-C, and non-HDL-C at baseline [20] and with progression from normal to abnormal over time [44]. Intensive insulin therapy has been shown to improve endothelial function and microvascular reactivity in children and adolescents with T1DM independently of changes in HbA1c [45].

In a longitudinal study of 1478 youth with T1D (age 10.8 years ± 3.9 years, 50% male, 77% non-Hispanic white, not on lipid-lowering medications at baseline) enrolled in the SEARCH for Diabetes in Youth study, increase in HbA1c was associated with progression of non-HDL-C from normal to abnormal levels [44]. Similarly, among 212 youth with T2D enrolled in the SEARCH for Diabetes in Youth study who had lipid levels assessed at baseline and after an average of 7 years of follow-up, each 1% increase in HbA1c AUC was associated with a 13% higher risk of progression and abnormal TG levels that persisted at follow-up and a 20% higher risk of progression and abnormal LDL-C that persisted at follow-up [46]. In youth with T1D, a 2% decrease in HbA1c 2 years after the initial blood test (from 10% to a HbA1C of 8%) was calculated to result in a TC decrease of 11.4 mg/dL, LDL-C decrease of 9 mg/dL, non-HDL-C decrease of 12.4 mg/dL, improved HDL-C by 1.3 mg/dL, and 8.5% overall decrease in TG [47]. In summary, though worsening of glycemic control is associated with increase in lipids, the magnitude of change in lipids following improvement in glycemic control has been modest and this strategy alone may be insufficient to reach optimal lipid levels in youth with hyperlipidemia.

Medical Nutrition Therapy

The components of the nutrition therapy for hyperlipidemia include limiting the amount of calories from fat to 25–30%, saturated fat less than < 7% of total calories, dietary cholesterol < 200 mg/day, avoidance of trans fats, and limiting to approximately 10% calories from monounsaturated fats [38]

Weight Management

Obesity is a risk factor for hyperlipidemia in youth with T1D [29, 44]. Increased waist-to height ratio has been associated

Table 3 Treatment recommendations for hyperlipidemia in youth with diabetes

Lipid goals	LDL-C < 100 mg/dL HDL-C > 35 mg/dl Triglycerides < 150 mg/dl
Initial measures	Optimize glycemic control Weight management Physical activity (60 min of moderate or vigorous aerobic activity daily) plus vigorous muscle strengthening and bone strengthening activities at least 3 days per week
Initial Nutrition therapy	Limit calories from fat to 25–30% Saturated fat < 7% of total calories Dietary cholesterol < 200 mg/day Avoid trans fats 10% calories from monounsaturated fats Decrease simple sugar intake and increase omega 3 fatty acids intake if TG elevated
Statins	≥ 10 years of age with LDL-C > 160 mg/dL or > 130 mg/dL with additional risk factors despite other measures

LDL-C, low-density lipoprotein cholesterol; *HDL-C*, high-density lipoprotein cholesterol [38, 39]

with progression of non-HDL-C from normal to abnormal values [44]. In a study of 1142 youth with incident T1D, who had at least two fasting lipid measurements over 2 years (initial visit mean: age = 10.8 ± 3.9 years, body mass index (BMI) z = 0.55 ± − 0.97, T1DM duration = 10.7 ± 7.6 months; 47.5% female, 77.9% non-Hispanic white) in the SEARCH for Diabetes in Youth Study [51], decreases in BMI z were associated with favorable changes in HDL-C and TG and the magnitude of these changes depended on the initial BMI z value so that greater improvements were seen in those with higher BMI z. Therefore, weight loss is helpful in improving lipids in youth with T1D.

Youth with T2D and severe obesity experience significant improvement in hyperlipidemia following bariatric surgery (laparoscopic sleeve gastrectomy and Roux-en-Y gastric bypass) [52–54]. Bariatric surgery also results in significant improvement or remission of T2D. Current guidelines by The American Society for Metabolic and Bariatric surgery and by the American Academy of Pediatrics recommend consideration of bariatric surgery in adolescents with severe obesity that also have T2D and hyperlipidemia after an initial trial of lifestyle interventions [55, 56].

Physical Activity

The ADA and ISPAD recommend 60 min of moderate (e.g., brisk walking, dancing) to vigorous (e.g., running, jumping rope) intensity aerobic activity daily. Vigorous muscle strengthening and bone strengthening activities are recommended at least 3 days per week [38, 40]. Physical activity has been shown to be associated with modest improvement in lipid levels (decrease in LDL-C and TG and increase in HDL-C) in patients with both T1D and T2D [57, 58]. Various studies in adults with diabetes demonstrate decrease in LDL-C by 8–14% and TG by 13–15% with exercise [59]. These effects are independent of the changes in glycemic control and may be more pronounced in those with an adverse lipid profile [59]. In a prospective randomized clinical trial in youth with T1D in Egypt (males, age 14.78 ± 2.31 years), participants that participated in exercise sessions (one exercise session per week and three exercise sessions per week) had improvements in LDL-C (from 101 ± 37.8 to 89 ± 33.4 mg/dL and from 132.2 ± 34 to 102.7 ± 27 mg/dL, $P = 0.01$, $P = 0.001$ respectively) whereas the control group (no exercise) did not have these improvements (94.3 ± 22.8 to 95 ± 22.37 mg/dL, P = 0.45 [60]. HDL-C increased in both exercise groups, but not in the control group. Exercise has also been associated with improvements in LDL-C, TG and HDL-C in children with obesity [61].

In summary, physical activity has been shown to result in modest improvement in lipid levels in patients with diabetes, though data specifically in youth are limited. Exercise therefore is an important component of behavioral strategies that can play an role in cardiovascular health with improvement of LDL-C, HDL-C, and TG levels.

Statins

Statins are recommended as first-line therapy for persistent hyperlipidemia despite dietary modifications and lifestyle interventions in youth with both T1D and T2D [38–40, 62, 63]. Statins are HMG CoA reductase inhibitors and are approved by the Food and Drug Administration (FDA) for children with familial hypercholesterolemia. Rosuvastatin is approved for homozygous familial hypercholesterolemia in children 7 years and older. Pravastatin, pitavastatin, and rosuvastatin are approved for heterozygous familial hypercholesterolemia in children 8 years of age and older and atorvastatin, pravastatin, fluvastatin, simvastatin, and lovastatin are approved for heterozygous familial hypercholesterolemia children 10 years of age and older. The recommendations for use of statins in youth with diabetes are based on data extrapolated from youth with familial hypercholesterolemia. In a 20-year follow-up study of children with familial hypercholesterolemia, statin therapy was noted to reduce the risk of CVD in adulthood and slow the progression of carotid intima-media thickness [64]. Several studies in children with familial hypercholesterolemia have demonstrated that statins slow the progression of subclinical atherosclerosis measured as carotid intima media thickness or flow mediated dilation [65–68]. Statins have been shown to result in a 25–40 mg/dL reduction in LDL-C level on an average [69]. Statins have been associated with increased risk for myopathy in adults with T2D. However, these adverse effects have not been demonstrated in pediatric studies. The benefits of statin treatment in youth with diabetes are not likely to be apparent for several decades, and therefore, statins should not be withheld due to lack of data demonstrating their benefit in short-term studies. In a recent multinational study of youth with T1D, statin therapy was effective in decreasing LDL-C but did not impact carotid intima media thickening [70]. There are currently no data on the impact of statin therapy on lipid levels or markers of subclinical atherosclerosis in youth with T2D.

Challenges and Opportunities to Improve Hyperlipidemia Treatment in Youth with Diabetes

The data from various studies demonstrate that clinicians continue to lag in providing aggressive therapy for hyperlipidemia in youth with diabetes [18, 19, 23, 71, 72]. In a survey of 207 practicing clinicians for youth with T1D (members of the ADA Diabetes in Youth Special Interest

Group, Pediatric Endocrine Society or T1D Exchange), only 6–17% reported lifestyle and nonmedical recommendations (e.g., improving glycemic control) as being effective in managing dyslipidemia or hypertension while most providers described medications as often effective [73]. However, only three quarter (76%) of providers stated they would start a lipid-lowering medication for LDL-C above 160 mg/dL that persisted after 6–12 months of lifestyle efforts and improving glycemic control. If the levels were between 130 and 160 mg/dL after 6–12 months of non-pharmacological intervention, only almost half (56%) would start a statin in those with additional risk factors for CVD [73]. Only 57% reported titrating lipid-lowering medications to the reported target of < 100 mg/dL. Therefore, a significant proportion of specialists caring for youth with diabetes reported not following the guidelines for treatment of hyperlipidemia.

One major challenge which appears to impede aggressive management of hyperlipidemia by clinicians for youth with diabetes is the lack of data on long-term safety and cardiovascular outcome efficacy of lipid-lowering therapy in youth with diabetes. This data would be improbable in the short term and midterm and can be derived only from long-term observational data that could take several decades. The current treatment guidelines are based on data extrapolated from children with familial hypercholesterolemia or adults with diabetes [74]. Data in adults with diabetes are limited as well. In adults with T1D, a randomized placebo-controlled trial demonstrated that statin therapy with simvastatin decreased the risk of having a major vascular event in diabetics even in the absence of manifest coronary disease or high cholesterol concentration [74]. There is not enough data at this time regarding the number of children and adolescents that would need to be treated to prevent an event. The absence of any signs of CVD during childhood and onset of events after several decades in adult life is a factor contributing to delay in initiation of lipid-lowering medications in youth with diabetes.

The addition of lipid-lowering-treatment may be perceived as an additional burden (self-management and financial) by clinicians as well as by youth and their families. Diabetes-related self-management tasks and costs of diabetes medications and supplies are a major burden for youth/families with diabetes, and clinicians may be hesitant to add to these challenges by adding a statin or suggesting nutrition therapy. Another challenge to aggressive dietary management of hyperlipidemia in youth with diabetes is the data from adult studies that show improvement in HbA1c with low carbohydrate diets in adults [75]. Excellent glycemic control was reported by children and adults with T1D on very low carbohydrate diet [49]. This may be challenging for lipid management in that low carbohydrate diets often end up containing more fat than is recommended in AHA Step 2 diet and may worsen hyperlipidemia.

Another barrier that prevents an aggressive approach to hyperlipidemia in youth with diabetes may be the expectation of clinicians and patients/families that lipids may improve over time. However among 1478 youth with T1D (age 10.8 ± 3.9 years, 50% male, 77% non-Hispanic white, not receiving lipid-lowering medications) at baseline and at a mean follow-up of 7.1 ± 1.9 years in the SEARCH for Diabetes in Youth study, regression from an abnormal non HDL-C (defined as > 130 mg/dL) to normal non HDL-C was seen in only 5% and instead progressed from normal to abnormal non HDL-C in 19% [44]. Provider education regarding the natural history of lipids in youth with diabetes is an important component of any efforts to improve management of hyperlipidemia.

A multi-pronged approach is essential to improve the rates of screening and management of hyperlipidemia in youth with diabetes (Fig. 1). A survey-based study of providers for children with diabetes in England, Northern Ireland, and Wales noted that only 14% of clinicians had recommended a statin in the last 5 years [76]. In another study of pediatric primary care providers, the majority (83%) were uncomfortable managing lipid disorders, and 57% were opposed to the use of lipid-lowering medications in children [77]. These barriers may be the consequence of knowledge gaps and concerns about the side effects or efficacy of statins for improving cardiovascular health specifically in youth. Continuous medical education regarding guidelines for treatment of hyperlipidemia and data on use of statins in youth should be provided to clinicians caring for youth with diabetes.

Point of care diabetes clinical decision support tools can be helpful in improving screening rates and allow identification of abnormal results using alerts [78, 79]. Electronic alerts of abnormal values have also been shown to improve treatment of hyperlipidemia in adults [80]. These clinical decisions support tools and alerts may allow for better care coordination in busy outpatient practices. Continuous quality improvement projects assessing rates of screening and treatment are another strategy that can help with timely and appropriate management of hyperlipidemia in this high-risk population.

Buy-in from youth and their families is essential for successful treatment of hyperlipidemia in youth with diabetes. Improving awareness of youth and their families of the risk for CVD due to diabetes and the additional impact of hyperlipidemia on that risk can help in improving patient and family compliance with management of hyperlipidemia. In a study using semi-structured interviews of teens with T1D and their parents, barriers identified to optimal health included limited teen knowledge about dyslipidemia, an obesity-promoting environment and parental distrust of medications [81]. Strategies suggested to manage CVD risk factors included specific and realistic guidance from providers, family support of teen lifestyle management, and having exercise partners.

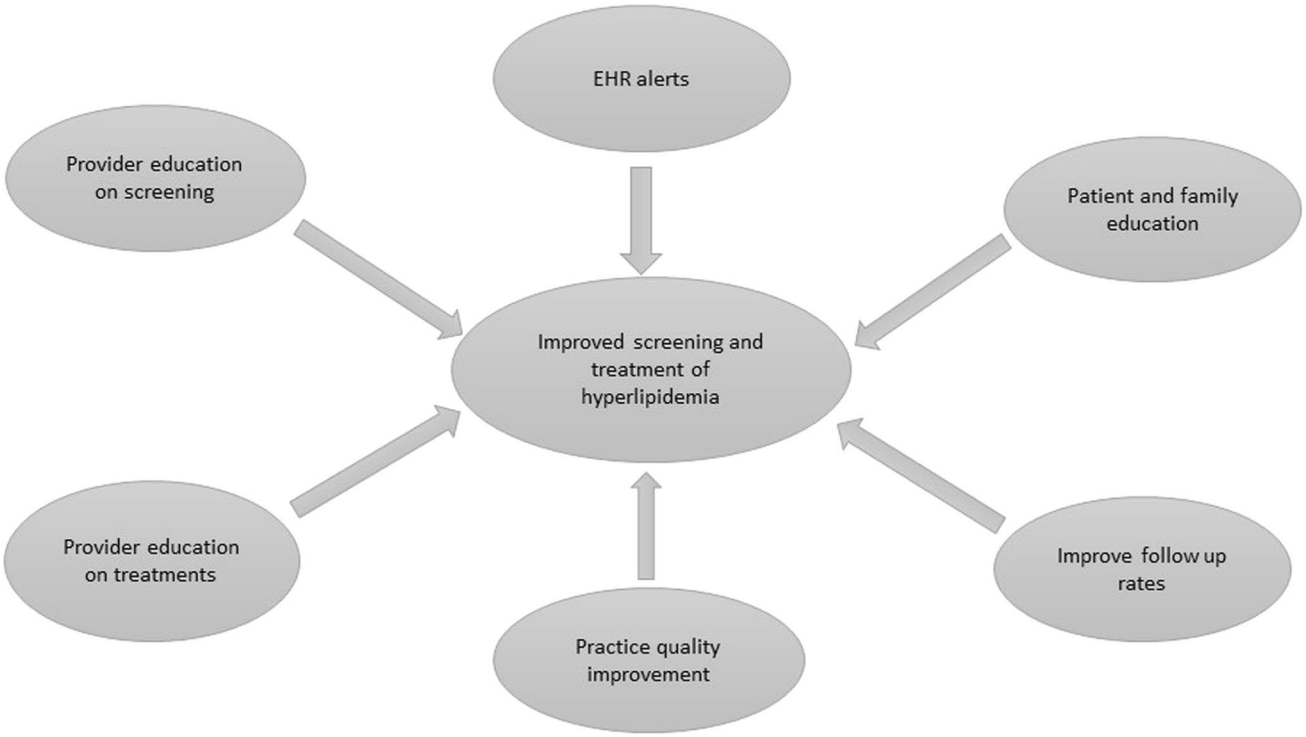

Fig. 1 Strategies to improve hyperlipidemia screening and treatment in youth with diabetes

Conclusion

Hyperlipidemia is prevalent in youth with T1D and T2D. However, hyperlipidemia remains undertreated in a significant proportion of youth with diabetes. Statins are recommended for management of persistent hyperlipidemia after optimizing glycemic control, nutritional therapy, and lifestyle modifications. Further studies are needed to assess the long-term data on statin safety and efficacy for CVD prevention in youth with diabetes and these may influence willingness of clinicians to aggressively manage hyperlipidemia in this population. Other efforts to improve management of hyperlipidemia in this population may include continued health care provider and patient education, developing EHR alerts and quality improvement for screening and treatment. Sustained efforts in improving hyperlipidemia recognition, research, and management in youth living with diabetes will hopefully ultimately translate to improved morbidity and mortality rates for this population later in adult life.

Declarations

Conflict of Interest The authors have no competing interests to declare that are relevant to the content of this article.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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• Of importance
•• Of major importance

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