**CARDIOVASCULAR RISK REDUCTION IN YOUTH WITH DIABETES- OPPORTUNITIES AND CHALLENGES**

**Amy S. Shah, MD, MS.** Department of Pediatrics. Division of Endocrinology, 3333 Burnet Ave, ML 7012, Cincinnati Children’s Hospital Medical Center & the University of Cincinnati, Cincinnati, OH, 45229, USA. Fax: 513-803-1174, Phone: 513-636-4744. Email: amy.shah@cchmc.org

**Don P. Wilson, MD, FNLA**. Department of Pediatric Endocrinology and Diabetes, Cook Children's Medical Center, Fort Worth, TX, USA. Don.Wilson@cookchildrens.org

**Received June 19, 2024**

**ABSTRACT**

Despite a notable decline over the past few decades, cardiovascular disease (CVD) remains the leading cause of premature mortality in individuals with diabetes mellitus. Compared to individuals without diabetes, there is ~2-fold or higher increase in CVD and mortality in those with diabetes. While CVD-related complications are seen predominantly during adulthood, the atherosclerotic process begins in childhood and is accelerated in individuals with type 1 diabetes (T1D), and even more so in type 2 diabetes (T2D). While there are improved methods of achieving glycemic control, earlier recognition and management of CVD risk factors, and advances in treatment, an increase in the prevalence of both T1D and T2D among youth continues to present additional challenges, especially because newer medications are underutilized. In this review, we discuss the origin and progression of atherosclerosis in youth with both T1D and T2D, CVD risk factors, and current guidelines. We conclude with key clinical questions that urgently need to be addressed to increase risk factor screening rates and treatment to improve outcomes in this high-risk population.

**INTRODUCTION**

Cardiovascular disease remains the leading cause of premature mortality in individuals with diabetes (1, 2). There is ~2-fold increase in CVD and premature mortality in those with versus those without diabetes (3-5). Moreover, the incidence and prevalence of diabetes continues to increase, both in adults and children. It is estimated that by 2025, 1.3 billion individuals are projected to have diabetes worldwide.In addition to the individual burden of this disease, diabetes increases health care utilization and costs. Despite these challenges, within the past two decades there has been a significant reduction in all-cause and CV-related mortality in this population (6). When CV risk factors (hemoglobin A1c, LDL cholesterol, albuminuria, smoking and blood pressure) are within the target ranges, risk of death, myocardial infarction, or stroke appears similar to the general population (6).

**TYPES OF DIABETES IN YOUTH**

T1D results from destruction of pancreatic beta-cells, secondary to an autoimmune process. It is characterized by dysregulation of plasma glucose, resulting in chronic hyperglycemia. An inability to secrete insulin necessitates exogenous insulin to maintain normal or near-normal levels of plasma glucose. Improved formulations of insulin, automated delivery systems, and continuous glucose monitoring devices have significantly improved the management of T1D.

T2D likely results from a combination of genetic, environmental, and metabolic risk factors. The pathophysiology of youth-onset T2D includes hepatic, peripheral, and adipose tissue insulin resistance together with relative insulin deficiency due to impaired pancreatic beta (β)-cell function (6-9), hyperglucagonemia due to alpha (α)-cell dysfunction, and impaired incretin effect (10). While youth share similar pathophysiological features with adults with T2D, some unique characteristics have been identified in youth. Youth with T2D have greater insulin resistance (11, 12), more rapid pancreatic beta cell decline, and poorer responses to diabetes medications compared to adults (13-17). In the last five years, medications including glucagon like peptide-1 receptor agonists and sodium-glucose transport protein 2 inhibitors have been approved for use in pediatric patients. Interested readers can find more information about the pathophysiology and types of diabetes at Endotext: Etiology and Pathogenesis of Diabetes Mellitus in Children and Adolescents. 2021 Jun 19. PMID: 29714936.; Pathogenesis of Type 2 Diabetes Mellitus. 2021 Sep 27. PMID: 25905339 (18).

There are other types of diabetes that develop in childhood including monogenic forms of diabetes, diabetes secondary to medications (e.g steroids), and diabetes associated with exocrine pancreas dysfunction (cystic fibrosis-related diabetes). CVD risk in these rare forms of diabetes is relatively unknown and, therefore, not the focus of this chapter. Interested readers can find more information about atypical forms of diabetes at Endotext: Atypical Forms of Diabetes. 2022 Feb 24. PMID: 25905351 (19).

**EPIDEMIOLOGY**

Among youth 19 years-of-age or younger, 7,759 in a population of 3.61 million in 2017 had T1D i.e. a prevalence of approximately 1:500.This represents an increase of 45.1% (95% CI, 40.0%-50.4%) from 2001 (20). The greatest absolute increases were observed among non-Hispanic White (0.93 per 1000 youth [95% CI, 0.88-0.98]) and non-Hispanic Black (0.89 per 1000 youth [95% CI, 0.88-0.98]) (20). The increased incidence of T1D in children 5 years-of-age and younger is of particular concern, since adverse CVD outcomes are associated with duration of diabetes (21).

Among youth 10 to 19 years-of-age, 1,230 in a population of 1.85 million in 2017 had T2D. This represents a prevalence of ~1:1500 and an increase of 95.3% (95% CI, 77.0%-115.4%) from 2001. The increase largely parallels the rise in childhood obesity. The incidence of T2D from 2002 to 2012 differed across race/ethnic groups with the largest increases observed in non-Hispanic Black, Native American, and Asian/Pacific Islander youth, followed by Hispanic youth, with a low and stable incidence in non-Hispanic White youth.

**CARDIOVASCULAR DISEASE RISK IN YOUTH WITH DIABETES**

It is estimated that 14-45% of children with T1D have at least 2 CVD risk factors and this risk increases with age (22); 32% of youth with T2D had ≥2 and 32% had ≥3 CVD risk factors. The two most common CVD risk factors independent of diabetes type were increased waist circumference and low HDL-C, despite the traditional presentation of T1D thought to be in youth without obesity. The SEARCH for Diabetes in Youth study found participants with youth-onset T2D were 5-fold more likely to have ≥2 CVD risk factors, relative to T1D participants (OR = 5.1 [4.8, 5.4], P < 0.0001) (23).

Long term observational data from Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study found 60% of young adults with youth-onset T2D had ≥1 microvascular complication by a mean age of 26 years and 17/500 youth had already experienced a serious cardiovascular event (myocardial infarction [4 events], congestive heart failure [6 events], coronary artery disease [3 events], and stroke [4 events]) (24). Observations from the SEARCH for Diabetes in Youth study have shown microvascular complications, including diabetes-related kidney disease, retinopathy, and peripheral neuropathy, are >2-fold higher in youth with T2D compared to T1D, though complications were frequent in both teenagers and young adults with T1D and T2D (25).

The presence of CV risk factors in diabetes, including dyslipidemia, hypertension, and adiposity, confers an increased risk of myocardial infarction (MI), stroke, incident peripheral arterial disease, heart failure hospitalization, and CV death that increases with age (26). While the latter events occur during adulthood, their origins begin much earlier. Ample evidence supports the presence of atherosclerosis, the underlying origin of CVD, beginning in childhood, and is accelerated in youth with T1D and T2D (27).

Although randomized controlled trials (RCT) have conclusively demonstrated that intense glycemic control can reduce the risk of microvascular complications in both T1D and T2D (28), the relationship of glycemia per se to macrovascular risk in diabetes has been mixed (29). Risk factors other than hyperglycemia (e.g. hypertension, dyslipidemia, overweight/obesity, chronic inflammation, and renal impairment) are key determinants of atherosclerotic cardiovascular disease (ASCVD) event risk and often precede the onset of hyperglycemia, especially in T2D (30, 31). Additionally, chronic hyperglycemia, if present, is strongly associated with worsening of retinopathy, neuropathy, and nephropathy (32). There may also be aspects of less-than-ideal medication adherence which also contribute to higher CVD risk (33). Reduction in ASCVD related morbidity and mortality is possible with early identification and aggressive management of concomitant risk factors (34-36). Further, optimal glycemic control, is helpful to achieve better clinical outcomes in both T1D and T2D (6).

To improve outcomes for youth with diabetes, global risk factor screening, including assessment of modifiable and non-modifiable risk factors (enhancers), health behaviors and social determinants of health (Figure 1) screening should be performed to help appropriately categorize risk and define targets for early intervention. Particularly concerning are genetic disorders, such as familial hypercholesterolemia (FH) and elevated levels of lipoprotein (a) which, when present, result in lifetime exposure to atherogenic lipoproteins and a significant increase in CVD risk independent of diabetes (37, 38).



**Figure 1. Global risk factors associated with cardiovascular disease. Adapted from (39).**

**Non-Modifiable Risk Factors**

Risk factors for CVD are generally classified as non-modifiable or modifiable. Non-modifiable risk factors are those that cannot be changed. These include sex, race/ethnicity, and family history of premature CVD. There is evidence that the in-utero environment (gestational diabetes, maternal hypercholesterolemia), low birth weight, and polygenic risk factors play a significant role in the future CVD risk of a child. While non-modifiable risk factors are not amenable to therapy, their presence suggests the need for early identification and optimal management of modifiable risk factors.

**Modifiable Risk Factors**

CV biomarkers, such as lipids and lipoprotein levels are commonly used to assess risk and serve as therapeutic targets. Published guidelines provide recommendations for initial and follow-up measurements of key CV risk factors in youth with diabetes, as well as goals to achieve optimum health (40, 41). While an in-depth discussion of modifiable risk factors is beyond the scope of this review, several highlights by diabetes type are discussed below and in the Table 1.

|  |
| --- |
| **Table 1. Recommendations for Cardiovascular Risk Factor Screening in Youth with Diabetes** |
| **Risk Factor** | **Recommendations for T1D**  | **Differences for T2D** | **Goals** | **Comments** |
| **Hyperglycemia** | Real-time CGM or intermittently scanned CGM should be offered Glycemic status should be assessed at least every 3 monthsAutomated insulin delivery systems may be considered to improve glycemic control. | Glycemic status should be assessed at least every 3 monthsReal-time CGM or intermittently scanned CGM should be offered when on multiple daily injections or on continuous subcutaneous insulin infusion  | An A1C of <7% is appropriate for many children and adolescents with T1D and T2D. In T1D an A1c target of 7.5 or 8% may be appropriate for selected individuals. In T2D an A1c target <6.5% may be appropriate for selected individuals. | A1c targets need to consider risk of hypoglycemia and be adjusted accordingly.  |
| **Dyslipidemia** | Initial lipid profile should be performed soon after diagnosis, preferably after glycemia has improved and age is ≥2 years. If initial LDL-C is ≤100 mg/dL (2.6 mmol/L), subsequent testing should be performed at 9-11 years of age. If LDL-C values are within the accepted risk level (<100 mg/dL [2.6 mmol/L]), a lipid profile repeated every 3 years is reasonable. | Initial lipid profile should be performed soon after diagnosis, preferably after glycemia has improved. If LDL-C values are within the accepted risk level (<100 mg/dL [2.6 mmol/L]), a lipid profile repeated annually. | LDL-C value <100 mg/dL (2.6 mmol/L). Non-HDL-C level has been identified as a significant predictor of the presence of atherosclerosis—as powerful as any other lipoprotein cholesterol measure in children and adolescents. Non-HDL-C target is <130mg/dL | Initial testing may be done with a non-fasting lipid level with confirmatory testing with a fasting lipid panel. Children with a primary lipid disorder (e.g., familial hyperlipidemia) should be referred to a lipid specialist. A major advantage of non-HDL-C is that it can be accurately calculated in a non-fasting state and therefore is practical to obtain in clinical practice as a screening test |
| **Blood Pressure**  | BP should be measured at every routine visit. | Same as T1D | BP <90th percentile for age, sex, and height or, in adolescents aged ≥13 years, <130/80 mmHg. | In youth with high BP (≥90th percentile for age, sex, and height or, in adolescents aged ≥13 years, BP ≥120/80 mmHg) on three separate measurements, ambulatory BP monitoring should be strongly considered. |

Abbreviations: BP, blood pressure; GFR, glomerular filtration rate; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Non-HDL-C, non-high-density lipoprotein cholesterol; T1D, type 1 diabetes mellitus

HYPERGLYCEMIA

Although glycemic control is critically important in managing diabetes, data linking improved glycemic control to a reduction in macrovascular complications are limited (27). Nonetheless, compared to those receiving standard care, CVD events in individuals with T1D who received intense insulin treatment at diabetes onset were reduced by 42% (95% CI, 9-63%) and the combined end-point of non-fatal MI, stroke or mortality by 57% (95% CI, 12-79%), despite similar treatment and glycemic control after completion of the study (42, 43). Similarly, results from the UK Prospective Diabetes Study (UKPDS) (44) and its 10-year cohort follow-up (45) suggest that intensive glucose control may be of greater CVD benefit when initiated early in T2D. One study found a 1% increase in HbA1c was associated with a 6-fold increase in coronary artery stenosis (46). In youth with diabetes, noninvasive measures of subclinical CVD, such as arterial stiffness and carotid intima media thickness (cIMT) are correlated with glycemic control (46-51). While hyperglycemia promotes endothelial dysfunction and arterial stiffness, there is growing evidence that optimum glycemic control alone is insufficient to significantly reduce the burden of CVD in persons with diabetes (52, 53). Glycemic recommendations for youth with diabetes are shown in Table 1.

DYSLIPIDEMIA

There is a high prevalence of dyslipidemia in adolescents with T1D; with 24-35% estimated to have hypercholesterolemia (54, 55). In the SEARCH for Diabetes in Youth study, approximately 15% of youth with T1D had high triglycerides,10% with low HDL-C and 10% with elevated apoB levels (56). In youth with T2D, 65% had elevated triglyceride levels, 60% had low HDL-C levels and 35% had elevated apoB levels. In a Denver cohort of youth, Maahs et al. demonstrated sustained abnormalities of total cholesterol, HDL-C and LDL-C over 10 years in children and adolescents with T1D, with 28% and 11 % having LDL-C levels ≥160 and 190 mg/dL, respectively. They also reported that 40-63% of childhood lipid abnormalities track from childhood to adulthood (57). In a retrospective analysis by Pelham et al, higher hemoglobin A1c levels were associated with higher LDL-C and apoB levels in youth with type 2 (58). Moreover, youth with T2D who had hemoglobin A1c levels of greater than 8% had significantly higher total cholesterol, LDL-C, and apoB levels compared to youth whose hemoglobin A1c levels were <8% (58).

The adverse vascular effects of prolonged exposure to atherogenic lipoproteins are well known and likely contribute to the subclinical atherosclerosis at an early age and accelerated in youth with diabetes (59). The current LDL-C goal of < 100 mg/dL (< 2.6 mmol/L) is supported by data in adults with childhood onset T1D which show that LDL-C levels of > 100 mg/dL are associated with increased CVD (54). Currently, guidelines for youth with diabetes do not recommend screening or treatment for apoB or lipoprotein (a) concentrations. Lipid recommendations are shown in Table 1. Interested readers can find more information about the roles of lipid and lipoprotein atherosclerosis atEndotext [Internet]: Linton MF, Yancey PG, Davies SS, Jerome WG, Linton EF, Song WL, Doran AC, Vickers KC. The Role of Lipids and Lipoproteins in Atherosclerosis. PMID: 26844337 (19).

There has been one RTC evaluating atorvastatin 10mg in youth 10-16 years of age with T1D. Compared to placebo, in the statin treated group there was a significant reduction in total, LDL-C, and non-HDL-C levels as well as in triglyceride levels, and in the ratio of apolipoprotein B to apolipoprotein A1. Of note, statin use during 48 months of the trial was not associated with differences between groups in carotid intima-media thickness (cIMT), glomerular filtration rate, or progression of retinopathy (60).

HYPERTENSION

Hypertension in youth with diabetes is common, with an estimated prevalence of 4-7% in youth with T1D (61); and 25-40% in those with T2D (62). In the TODAY study baseline prevalence of hypertension among youth with T2D was 19.2%. Over 14- years the cumulative incidence was 59.2%. Males were at higher risk of developing hypertension as were non- Hispanic whites compared with Hispanic youth (63). Hypertension is likely under-recognized, in part related to the challenges of measuring blood pressure in an ambulatory setting. Increases in arterial stiffness and cIMT have been observed in the setting of hypertension (2, 62), and correlate with the progression of diabetic nephropathy (64). While there are data that support hypertension-related target organ damage beginning in youth, CV clinical trials with measures of hard outcomes, such as fatal and non-fatal MI and stroke, are lacking in children. Nonetheless, current guidelines recommend blood pressures of < 90th percentile for age, sex and height (<120/80 if over age 13 years) and intervention when higher BP levels are sustained,Table 1.

OVERWEIGHT AND OBESITY

The prevalence of obesity (BMI > 95th percentile), a known risk factor for CVD, has been estimated to be 4.4-25% in T1D youth (65-67). T1D youth with obesity have a higher prevalence of hypertension, metabolic syndrome, and elevated alanine aminotransferase than those with a normal BMI (68). Prevalence of obesity approaches ~80% among youth with T2D; ~10% being overweight (67). In the SEARCH for Diabetes in Youth study among children 3-19 years-of-age, the prevalence of a BMI >85th in those with diabetes was higher than those without diabetes. In a 20-year follow-up of 655 individuals with T1D, an age-independent increase in overweight/obesity was observed; the relationship of adiposity with mortality resembling that of the general population, albeit with a marked increased risk in those who are underweight (69). Increased food intake secondary to concerns of hypoglycemia and intense insulin regimens may also contribute to excessive weight gain (69). Compared with BMI or percent body fat, central adiposity may be a better predictor of cardiovascular risk (2, 70). Higher waist circumference is an independent risk factor of subclinical CVD (arterial stiffness and cIMT) in youth with diabetes (2, 47, 49, 71). Current guidelines utilize BMI targets for weight optimization.

**Health Behaviors and Conditions**

PHYSICAL ACTIVITY

Numerous studies have found that a sedentary lifestyle is a risk factor for future CVD. Moreover, physical activity is inversely related to hemoglobin A1c, occurrence of diabetic ketoacidosis, BMI, dyslipidemia, and hypertension as well as retinopathy and microalbuminuria (72). Conversely, interventions to increase physical activity have demonstrated positive effects on hemoglobin A1c, BMI, triglycerides, and total cholesterol (73); the most effective being interventions >12 weeks in duration, with 3 or more 60-minute sessions per week which include resistance and aerobic exercise (74). Exercise once a week for 30 minutes has also been reported to lower hemoglobin A1c and diastolic blood pressure and improve dyslipidemia (72). Regardless of diabetes type, current pediatric guidelines recommend 3 or more 60-minute sessions per week which include resistance training and aerobic exercise.

SMOKING

In adults, active as well as passive smoking has been shown to be major risk factor for CVD and associated with poor glycemic control, adverse changes in lipid profile, nephropathy, endothelial dysfunction, and vascular inflammation (75-77). Although limited, there are data that demonstrate similar findings in teens (77). The prevalence of smoking in children and young adults with T1D is estimated to be 3-28 %, with higher prevalence in those 15 years-of-age and older (2, 54, 78). In the TODAY study smoking incidence increased 6-fold over 14 year study with the average prevalence of 24% in youth 18 years and older (63). All youth should be encouraged to avoid/cease cigarette smoking, including electronic cigarettes.

KIDNEY DISEASE

The presence of target organ damage, particularly related to renal function, is a strong risk factor for CVD (1, 64). Persistent albumin excretion rate of 30 to 299 mg/24h and >300 mg/24hr are associated with CVD, and increased mortality with reduced glomerular filtration rates in individuals with T1D (79-81). Although the underlying mechanisms are incompletely understood, reduced glomerular filtration rate, independent of albuminuria, is also associated with increased risk of CVD (82, 83). Optimum control of modifiable risk factors, such as glucose, smoking, blood pressure, and dyslipidemia has been shown to reduce the incidence of both albuminuria and impaired renal function (28, 84-86). Interested readers can find more information about kidney disease in diabetes at Endotext [Internet]: Diabetic Kidney Disease. 2022 Aug 3. PMID: 25905328 (87).

MASLD

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a risk factor for ASCVD. MASLD is commonly associated with other CV risk factors including visceral adiposity, atherogenic dyslipidemia (low HDL-C, elevated triglycerides/remnant lipoproteins, and small dense low-density lipoprotein [LDL]), and insulin resistance with or without hyperglycemia (88). Although a portion of the risk is attributable to these comorbidities, a diagnosis of MASLD is associated with greater risk than the sum of these individual components (88).

FAMILIAL HYPERCHOLESTEROLEMIA (FH)

Youth with diabetes may also experience other independent health conditions associated with increased risk of CVD (89). For example, FH is a genetic disorder which is highly prevalent (1:200) in the general population and may coexist with diabetes. Although outcome studies are not available for children, adults with both diabetes and phenotypic FH had higher risk of CV mortality (T1D: hazard ratio 21.3 [95% CI 14.6–31.0]; T2D: 2.40 [2.19–2.63]) and of a CV event (T1D: 15.1 [11.1–20.5]; T2D: 2.73 [2.58–2.89]) compared to those with T1D and no FH. Further, patients with diabetes and phenotypic FH had increased risk of all major cardiovascular outcomes (p < 0.0001). These findings were observed despite a greater proportion of diabetes and phenotypic FH receiving lipid-lowering treatment (p < 0.0001) (90).

Of note, an association between T2D prevalence and FH has been reported. A cross-sectional study of 63,320 individuals who underwent DNA testing for FH in the Netherlands found the prevalence of T2D among those found to have FH was significantly lower than among unaffected relatives, with variability by mutation type. This finding, if confirmed, raises the possibility of a causal relationship between LDL receptor-mediated transmembrane cholesterol transport and T2D (91).

OTHER DISORDERS

Other chronic conditions known to be associated with CVD include connective tissue disorders, thyroid abnormalities, and acquired conditions, such as HIV/AIDS. In addition to accelerating risk, the presence of other health conditions may present unique challenges, including financial, psychosocial, relational, and quality of life. Keeping up with personal, social, and work demands is often challenging for young adults with one or more chronic conditions in addition to diabetes. Growing up with a chronic disease showed a lower likelihood of having a paid job (92), higher unemployment and sick leave rates compared to the general population (93, 94), and fatigue. (95, 96). Figure 2 below outlines several health conditions commonly associated with increased risk of premature CVD. Children with these conditions should be monitored frequently and abnormal values optimally managed to improve outcomes.



**Figure 2. Health Conditions Associated With Increased Risk of CVD (97). †Any moderate-risk condition with ≥2 additional risk enhancers. ‡Severe obesity is defined as BMI ≥99th percentile or ≥35 kg/m2, and obesity is defined as BMI ≥95th percentile to <99th percentile. §Defined as blood pressure >95th percentile or ≥130/80 mmHg on 3 separate occasions. ΔDefined as ≥3 risk enhancers. ‖ Involves obstructive lesions of the left ventricle and aorta, cyanotic congenital heart defects leading to Eisenmenger syndrome, and congenital coronary artery anomalies in isolation or in association with other congenital defects. ApoB, apolipoprotein B; BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease; DM, diabetes mellitus; ESRD, end-stage renal disease; FH, familial hypercholesterolemia; HeFH, heterozygous familial hypercholesterolemia; HIV, human immunodeficiency virus; HoFH, homozygous familial hypercholesterolemia; Lp(a), lipoprotein (a); MI, myocardial infarction.**

**Social Determinants of Health**

Social determinants of health (SDOH) play a major role in access to appropriate health care and clinical outcomes including CVD. These include food insecurity, housing instability, transportation barriers, low socioeconomic status, limited access to healthcare, early childhood adversity, and social isolation, all of which adversely influence the level and distribution of health within a society. Political systems and racism have been cited as upstream drivers of SDOH (98). Although recognized as obstacles, appropriate assessment and understanding of SDOH in youth with diabetes is limited, and strategies to improve health challenging. Lack of understanding of what interventions work, entrenched interests that benefit from health-harming aspects of the status quo, and the need to establish new mechanisms of finance for these programs have all made progress difficult (99).

In the U.S. T2D affects racial and ethnic minorities, including children, and low-income populations disproportionately, resulting in consistently higher risk of diabetes and rates of diabetes complications and premature mortality (100). Evidence supports an association of socioeconomic status (SES), neighborhood and physical environment, food environment, health care, and social context with diabetes-related outcomes. The living and working conditions and the environments in which children reside have a direct impact on biological and behavioral outcomes associated with diabetes prevention and control.

Food insecurity and adverse childhood experiences have been highlighted as important mediators of CVD in children (101, 102). For a comprehensive review, see <https://www.fao.org/publications/home/fao-flagship-publications/the-state-of-food-security-and-nutrition-in-the-world/2022/en>. Although food insecurity has been associated with the development of childhood obesity and cardiometabolic disease in adults, this relationship is inconsistent in youth (103, 104). While some studies have detected relationships, the National Human and Nutrition Examination Survey 2007-2012 (NHANES) in adolescents at or below 300% of the poverty line did not find a relationship between food insecurity and childhood CVD risk factors (105). Further analysis of these findings suggests that socio-ecological factors such as household income and parental education as well as individual level of physical activity, sedentary time, and smoking status may be interdependent mediators of CVD risk in youth. Youth and young adults with T1D and T2D report nearly twice the prevalence of food insecurity; predictors of household food insecurity include youth without insurance or receiving Medicaid or Medicare, level of parental education, and lower household income (106).

Adverse childhood experiences (ACEs) are also closely associated with poor cardiovascular outcomes with or without underlying food insecurity (107) resulting from 1) unhealthy behaviors such as physical inactivity, poor-quality diet, poor quality and duration of sleep, and smoking; 2) adverse physiologic mechanisms including inflammation and hypercortisolemia; 3) substance abuse and mental health disorders and mental health conditions such as depression and anxiety.

Current recommendations for the care of children with diabetes include assessing psychosocial concerns (e.g., diabetes distress, depressive symptoms, and disordered eating), family factors, and behavioral health concerns that could impact diabetes management. Health care professionals should also screen for food security, housing stability/homelessness, health literacy, financial barriers, and social/community support and incorporate that information in treatment decisions. Social workers and behavioral health professionals should be considered integral members of the pediatric diabetes interprofessional team to aid in screening, assessment and interventions (108).

**PRINCIPLE OF RISK FACTOR SCREENING AND MANAGEMENT**

Guidance for screening and management of youth with diabetes has been published by a number of professional organizations (40, 41). Cardiovascular risk in diabetes arises from microvascular and macrovascular pathology, as well as changes in cardiac structure and function. Therefore, the objectives of efforts to reduce CV risk are to maintain glycemic control, which is a key driver of microvascular complications and a contributor to macrovascular complications, as well as optimally managing cardiometabolic risk factors to reduce the risks for ASCVD and heart failure (26).

**Challenges to Cardiovascular Risk Reduction in Youth with Diabetes**

SCREENING

Despite evidence in youth with T1D and T2D demonstrating an increased prevalence of modifiable risk factors, and risk factors present at an early age predict premature CVD during adulthood, screening rates are less than ideal based on the limited available data. A study in the United Kingdom found 83.5% compliance with lipid screening in patients with T1D (109), while in children with T2D only half had lipid testing (68). In a survey of 1,514 US clinicians, blood pressure was stated to be measured at most or all visits in 95% and lipid screening in 88% of patients (although less frequently in older patients with T2D (69%) (110). When adherence to the International Society of Pediatric and Adolescent Diabetes (ISPAD) clinical practice guidelines was assessed for patients with T1D, two-thirds of physicians reported adherence to nephropathy and retinopathy screening and only half reported adherence to recommendations for neuropathy and macrovascular disease risk factors. Patient financial issues, the lack of laboratory resources and/or other equipment, and the need for referral were cited as the main reasons for variation in screening practices (111).

TREATMENT

Treatment with lipid lowering and blood pressure medications are low in pediatric patients with diabetes. When the SEARCH for Diabetes in Youth study examined their data in 2007, only 1% of T1D youth and 5% of T2D youth were on lipid lowering medications despite lipid abnormalities present in ~30-60% of youth (112). In 2020 the T1D Exchange Clinic Network (TIDX, US) and the Prospective Diabetes Follow-up Registry (DPV, Austria and Germany) examined medication use in young adults <26 years of age. Anti-hypertensive medication use was reported as 5% in T1DX and 3% in DPV and lipid lowering medication was 3% in the T1DX and 1% in DPV in those with T1D(113). Slightly higher medication use, but still low rates, were reported in the TODAY study cohort. Approximately half of the youth with hypertension were on blood pressure lowering medication and one third of those with a high LDL-C were on lipid lowering medication (63).

ACHIEVING TARGETS

Data were evaluated for 13,316 participants in the T1D Exchange clinic registry (<20 years old) to see how many youth and young adults with T1D met lipid, blood pressure, and BMI targets. Among participants with available data, 86% met HDL-C target of >40mg/dL, 65% had an LDL-C <100mg/dL, and 90% had triglycerides <150mg/dL. For blood pressure 78% had readings < 90th percentile for age, sex and height and 63% had a BMI of <85th percentile by CDC charts. Moreover, 17% of patients <18 years of age (in the 2016–2018 study) (114) and only 22% of children 6-12 years of age and 17% of children 13-17 years of age (in the 2010–2012 study) met the prior ADA A1C target of <7.5% (115). At the end of the TODAY study 73.2% of youth with T2D met optimal targets for blood pressure and 56.1% met optimal targets for LDL-C (63). Achieving targets in youth with T1D has been shown to be associated with greater insulin sensitivity, improved cardiopulmonary fitness (116), and cardiorenal protection at 2-year follow-up (117).

GUIDELINES AND RECOMMENDATIONS

Inconsistencies in pediatric versus adult guidelines for risk factor screening and management in individuals with diabetes creates challenges when children transition into adult health care. Complex treatment algorithms to determine the timing and frequency of risk factor assessment also appear to complicate screening of CV risk factors. Multiple guidelines for the identification and management CVD risk factors in youth with diabetes have been published (43, 118-122) with the goal of achieving CVD risk reduction. While some guidelines are applicable to all children, others specifically address risk assessment and management in those with diabetes. The latter contains unique recommendations based upon the type of diabetes, necessitating an accurate classification (i.e. T1D vs T2D). While highly desirable, differentiation between the diagnosis of T1D and T2D in youth can be challenging and not always performed/feasible in clinical practice. Although all published guidelines identify glycemic control, hypertension, and dyslipidemia as targets for CVD risk reduction, differences exist in optimum goals and approaches to risk factor reduction as outlined in Table 1.

Additional research is needed to understand the role of CVD risk factors in diabetes and identify barriers to screening and treatment in clinical practice. While the advantages of early CV risk reduction appear clear, there is also potential hesitancy due to unanswered questions. Ideally, professional societies and organizations would work together to provide viable solutions to several urgent clinical questions, Table 2.

|  |
| --- |
| **Table 2. Key Clinical Questions Regarding CV Risk Management and Treatment in Youth**  |
| Screening |
| * What is the ideal age to begin screening?
* Which CV risk factors should be measured and how often?
* If low risk (or values are normal), how often should risk factors measurements be repeated?
 |
| Management |
| * What BMI/waist circumference is ideal to aid in CV risk reduction?
* How do we define optimal therapeutic goals?
* What is the impact of MASLD and other diabetes related co-morbidities and complications?
* Should risk factor screening and management be the same for T1D and T2D?
* Should risk factor screening differ in children vs adults? What if there is concomitant FH?
 |
| Treatment |
| * Is lowering hemoglobin A1c, blood pressure and lipids enough to reduce CV risk and disease?
* What thresholds suggest the need for pharmacotherapy? Dose escalation? Dose reduction?
* Should certain risk factors be more aggressively targeted to reduce future CV risk and CVD?
 |
| Outcomes |
| * What are the barriers for risk factor screening and treatment?
* Would utilization of implementation science help increase screening rates?
* Can artificial intelligence analyze big data to determine what diabetes therapies achieve the best CV reduction?
 |

**CONCLUSION**

Individuals with diabetes have a 2-fold increase in CVD and premature mortality. Duration of diabetes is a predictor of premature mortality, placing youth at significant risk. Glycemic control alone appears to be insufficient to substantially reduce macrovascular complications, such as fatal and non-fatal MI and stroke. Global risk factor assessment and early intervention play a key role in reducing CVD-related risk and improving outcomes. While helpful, current recommendations for risk factor assessment and optimum management in youth are often inconsistent amongst published guidelines and the need for complex algorithms to determine the timing and frequency of risk factor assessment challenging. Additional research is needed to understand the role of CVD risk factors in youth-onset diabetes and identify barriers to screening and optimum management in clinical practice.

 **REFERENCES**

1. de Ferranti SD, de Boer IH, Fonseca V, Fox CS, Golden SH, Lavie CJ, et al. Type 1 diabetes mellitus and cardiovascular disease: a scientific statement from the American Heart Association and American Diabetes Association. Diabetes Care. 2014;37(10):2843-63.

2. Shah AS, Wadwa RP, Dabelea D, Hamman RF, D'Agostino R, Jr., Marcovina S, et al. Arterial stiffness in adolescents and young adults with and without type 1 diabetes: the SEARCH CVD study. Pediatr Diabetes. 2015;16(5):367-74.

3. Alman AC, Talton JW, Wadwa RP, Urbina EM, Dolan LM, Daniels SR, et al. Cardiovascular health in adolescents with type 1 diabetes: the SEARCH CVD study. Pediatr Diabetes. 2014;15(7):502-10.

4. Htay T, Soe K, Lopez-Perez A, Doan AH, Romagosa MA, Aung K. Mortality and Cardiovascular Disease in Type 1 and Type 2 Diabetes. Curr Cardiol Rep. 2019;21(6):45.

5. Krishnan P, Balamurugan A, Urbina E, Srinivasan SR, Bond G, Tang R, et al. Cardiovascular risk profile of asymptomatic healthy young adults with increased carotid artery intima-media thickness: the Bogalusa Heart Study. J La State Med Soc. 2003;155(3):165-9.

6. Rawshani A, Rawshani A, Franzén S, Eliasson B, Svensson AM, Miftaraj M, et al. Mortality and Cardiovascular Disease in Type 1 and Type 2 Diabetes. N Engl J Med. 2017;376(15):1407-18.

7. Hannon TS, Arslanian SA. The changing face of diabetes in youth: lessons learned from studies of type 2 diabetes. Ann N Y Acad Sci. 2015;1353:113-37.

8. Kim JY, Bacha F, Tfayli H, Michaliszyn SF, Yousuf S, Arslanian S. Adipose Tissue Insulin Resistance in Youth on the Spectrum From Normal Weight to Obese and From Normal Glucose Tolerance to Impaired Glucose Tolerance to Type 2 Diabetes. Diabetes Care. 2019;42(2):265-72.

9. Kim JY, Nasr A, Tfayli H, Bacha F, Michaliszyn SF, Arslanian S. Increased Lipolysis, Diminished Adipose Tissue Insulin Sensitivity, and Impaired β-Cell Function Relative to Adipose Tissue Insulin Sensitivity in Obese Youth With Impaired Glucose Tolerance. Diabetes. 2017;66(12):3085-90.

10. Michaliszyn SF, Mari A, Lee S, Bacha F, Tfayli H, Farchoukh L, et al. β-cell function, incretin effect, and incretin hormones in obese youth along the span of glucose tolerance from normal to prediabetes to type 2 diabetes. Diabetes. 2014;63(11):3846-55.

11. Metabolic Contrasts Between Youth and Adults With Impaired Glucose Tolerance or Recently Diagnosed Type 2 Diabetes: II. Observations Using the Oral Glucose Tolerance Test. Diabetes Care. 2018;41(8):1707-16.

12. Metabolic Contrasts Between Youth and Adults With Impaired Glucose Tolerance or Recently Diagnosed Type 2 Diabetes: I. Observations Using the Hyperglycemic Clamp. Diabetes Care. 2018;41(8):1696-706.

13. Effects of Treatment of Impaired Glucose Tolerance or Recently Diagnosed Type 2 Diabetes With Metformin Alone or in Combination With Insulin Glargine on β-Cell Function: Comparison of Responses In Youth And Adults. Diabetes. 2019;68(8):1670-80.

14. Hannon TS, Edelstein SL, Arslanian SA, Caprio S, Zeitler PS, Buchanan TA, et al. Withdrawal of medications leads to worsening of OGTT parameters in youth with impaired glucose tolerance or recently-diagnosed type 2 diabetes. Pediatr Diabetes. 2020;21(8):1437-46.

15. Shankar RR, Zeitler P, Deeb A, Jalaludin MY, Garcia R, Newfield RS, et al. A randomized clinical trial of the efficacy and safety of sitagliptin as initial oral therapy in youth with type 2 diabetes. Pediatr Diabetes. 2022;23(2):173-82.

16. Tamborlane WV, Barrientos-Pérez M, Fainberg U, Frimer-Larsen H, Hafez M, Hale PM, et al. Liraglutide in Children and Adolescents with Type 2 Diabetes. N Engl J Med. 2019;381(7):637-46.

17. Zeitler P, Hirst K, Pyle L, Linder B, Copeland K, Arslanian S, et al. A clinical trial to maintain glycemic control in youth with type 2 diabetes. N Engl J Med. 2012;366(24):2247-56.

18. Yau M, Maclaren NK, Sperling MA. Etiology and Pathogenesis of Diabetes Mellitus in Children and Adolescents. In: Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E, et al., editors. Endotext. South Dartmouth (MA): MDText.com, Inc. Copyright © 2000-2024, MDText.com, Inc.; 2000.

19. Feingold KR. Atypical Forms of Diabetes. In: Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E, et al., editors. Endotext. South Dartmouth (MA): MDText.com, Inc. Copyright © 2000-2024, MDText.com, Inc.; 2000.

20. Lawrence JM, Divers J, Isom S, Saydah S, Imperatore G, Pihoker C, et al. Trends in Prevalence of Type 1 and Type 2 Diabetes in Children and Adolescents in the US, 2001-2017. Jama. 2021;326(8):717-27.

21. Mayer-Davis EJ, Lawrence JM, Dabelea D, Divers J, Isom S, Dolan L, et al. Incidence Trends of Type 1 and Type 2 Diabetes among Youths, 2002-2012. N Engl J Med. 2017;376(15):1419-29.

22. Donaghue K, Jeanne Wong SL. Traditional Cardiovascular Risk Factors in Adolescents with Type 1 Diabetes Mellitus. Curr Diabetes Rev. 2017;13(6):533-43.

23. Kim G, Divers J, Fino NF, Dabelea D, Lawrence JM, Reynolds K, et al. Trends in prevalence of cardiovascular risk factors from 2002 to 2012 among youth early in the course of type 1 and type 2 diabetes. The SEARCH for Diabetes in Youth Study. Pediatr Diabetes. 2019;20(6):693-701.

24. Bjornstad P, Drews KL, Caprio S, Gubitosi-Klug R, Nathan DM, Tesfaldet B, et al. Long-Term Complications in Youth-Onset Type 2 Diabetes. N Engl J Med. 2021;385(5):416-26.

25. Dabelea D, Stafford JM, Mayer-Davis EJ, D'Agostino R, Jr., Dolan L, Imperatore G, et al. Association of Type 1 Diabetes vs Type 2 Diabetes Diagnosed During Childhood and Adolescence With Complications During Teenage Years and Young Adulthood. Jama. 2017;317(8):825-35.

26. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. 14. Children and Adolescents: Standards of Care in Diabetes-2023. Diabetes Care. 2023;46(Suppl 1):S230-s53.

27. Maahs DM, Daniels SR, de Ferranti SD, Dichek HL, Flynn J, Goldstein BI, et al. Cardiovascular disease risk factors in youth with diabetes mellitus: a scientific statement from the American Heart Association. Circulation. 2014;130(17):1532-58.

28. Reichard P, Nilsson BY, Rosenqvist U. The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. N Engl J Med. 1993;329(5):304-9.

29. Skyler JS, Bergenstal R, Bonow RO, Buse J, Deedwania P, Gale EA, et al. Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA diabetes trials: a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association. Diabetes Care. 2009;32(1):187-92.

30. Haffner SM, Stern MP, Hazuda HP, Mitchell BD, Patterson JK. Cardiovascular risk factors in confirmed prediabetic individuals. Does the clock for coronary heart disease start ticking before the onset of clinical diabetes? Jama. 1990;263(21):2893-8.

31. Viigimaa M, Sachinidis A, Toumpourleka M, Koutsampasopoulos K, Alliksoo S, Titma T. Macrovascular Complications of Type 2 Diabetes Mellitus. Curr Vasc Pharmacol. 2020;18(2):110-6.

32. Faselis C, Katsimardou A, Imprialos K, Deligkaris P, Kallistratos M, Dimitriadis K. Microvascular Complications of Type 2 Diabetes Mellitus. Curr Vasc Pharmacol. 2020;18(2):117-24.

33. Weinstock RS, Trief PM, Burke BK, Wen H, Liu X, Kalichman S, et al. Antihypertensive and Lipid-Lowering Medication Adherence in Young Adults With Youth-Onset Type 2 Diabetes. JAMA Netw Open. 2023;6(10):e2336964.

34. Ali MK, Bullard KM, Gregg EW. Achievement of goals in U.S. Diabetes Care, 1999-2010. N Engl J Med. 2013;369(3):287-8.

35. Buse JB, Ginsberg HN, Bakris GL, Clark NG, Costa F, Eckel R, et al. Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. Diabetes Care. 2007;30(1):162-72.

36. Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med. 2008;358(6):580-91.

37. Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. Eur Heart J. 2013;34(45):3478-90a.

38. Reyes-Soffer G, Ginsberg HN, Berglund L, Duell PB, Heffron SP, Kamstrup PR, et al. Lipoprotein(a): A Genetically Determined, Causal, and Prevalent Risk Factor for Atherosclerotic Cardiovascular Disease: A Scientific Statement From the American Heart Association. Arterioscler Thromb Vasc Biol. 2022;42(1):e48-e60.

39. Peterson AL, McNeal CJ, Wilson DP. Prevention of Atherosclerotic Cardiovascular Disease in Children with Familial Hypercholesterolemia. Curr Atheroscler Rep. 2021;23(10):64.

40. Shah AS, Zeitler PS, Wong J, Pena AS, Wicklow B, Arslanian S, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Type 2 diabetes in children and adolescents. Pediatr Diabetes. 2022;23(7):872-902.

41. 14. Children and Adolescents: Standards of Care in Diabetes-2024. Diabetes Care. 2024;47(Suppl 1):S258-s81.

42. Nathan DM, Genuth S, Lachin J, Cleary P, Crofford O, Davis M, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329(14):977-86.

43. Management of dyslipidemia in children and adolescents with diabetes. Diabetes Care. 2003;26(7):2194-7.

44. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998;352(9131):837-53.

45. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008;359(15):1577-89.

46. Aepfelbacher FC, Yeon SB, Weinrauch LA, D'Elia J, Burger AJ. Improved glycemic control induces regression of left ventricular mass in patients with type 1 diabetes mellitus. Int J Cardiol. 2004;94(1):47-51.

47. Dabelea D, Talton JW, D'Agostino R, Jr., Wadwa RP, Urbina EM, Dolan LM, et al. Cardiovascular risk factors are associated with increased arterial stiffness in youth with type 1 diabetes: the SEARCH CVD study. Diabetes Care. 2013;36(12):3938-43.

48. Shah AS, Dolan LM, Kimball TR, Gao Z, Khoury PR, Daniels SR, et al. Influence of duration of diabetes, glycemic control, and traditional cardiovascular risk factors on early atherosclerotic vascular changes in adolescents and young adults with type 2 diabetes mellitus. J Clin Endocrinol Metab. 2009;94(10):3740-5.

49. Shah AS, El Ghormli L, Gidding SS, Bacha F, Nadeau KJ, Levitt Katz LE, et al. Prevalence of arterial stiffness in adolescents with type 2 diabetes in the TODAY cohort: Relationships to glycemic control and other risk factors. J Diabetes Complications. 2018;32(8):740-5.

50. Shah AS, El Ghormli L, Vajravelu ME, Bacha F, Farrell RM, Gidding SS, et al. Heart Rate Variability and Cardiac Autonomic Dysfunction: Prevalence, Risk Factors, and Relationship to Arterial Stiffness in the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) Study. Diabetes Care. 2019;42(11):2143-50.

51. Urbina EM, Dabelea D, D'Agostino RB, Jr., Shah AS, Dolan LM, Hamman RF, et al. Effect of type 1 diabetes on carotid structure and function in adolescents and young adults: the SEARCH CVD study. Diabetes Care. 2013;36(9):2597-9.

52. Lind M, Svensson AM, Kosiborod M, Gudbjörnsdottir S, Pivodic A, Wedel H, et al. Glycemic control and excess mortality in type 1 diabetes. N Engl J Med. 2014;371(21):1972-82.

53. Orchard TJ, Nathan DM, Zinman B, Cleary P, Brillon D, Backlund JY, et al. Association between 7 years of intensive treatment of type 1 diabetes and long-term mortality. Jama. 2015;313(1):45-53.

54. Margeirsdottir HD, Larsen JR, Brunborg C, Overby NC, Dahl-Jørgensen K. High prevalence of cardiovascular risk factors in children and adolescents with type 1 diabetes: a population-based study. Diabetologia. 2008;51(4):554-61.

55. Schwab KO, Doerfer J, Marg W, Schober E, Holl RW. Characterization of 33 488 children and adolescents with type 1 diabetes based on the gender-specific increase of cardiovascular risk factors. Pediatr Diabetes. 2010;11(5):357-63.

56. Hamman RF, Bell RA, Dabelea D, D'Agostino RB, Jr., Dolan L, Imperatore G, et al. The SEARCH for Diabetes in Youth study: rationale, findings, and future directions. Diabetes Care. 2014;37(12):3336-44.

57. Maahs DM, Wadwa RP, McFann K, Nadeau K, Williams MR, Eckel RH, et al. Longitudinal lipid screening and use of lipid-lowering medications in pediatric type 1 diabetes. J Pediatr. 2007;150(2):146-50, 50.e1-2.

58. Pelham JH, Hanks L, Aslibekyan S, Dowla S, Ashraf AP. Higher hemoglobin A1C and atherogenic lipoprotein profiles in children and adolescents with type 2 diabetes mellitus. J Clin Transl Endocrinol. 2019;15:30-4.

59. Urbina EM, Kimball TR, McCoy CE, Khoury PR, Daniels SR, Dolan LM. Youth with obesity and obesity-related type 2 diabetes mellitus demonstrate abnormalities in carotid structure and function. Circulation. 2009;119(22):2913-9.

60. Marcovecchio ML, Chiesa ST, Bond S, Daneman D, Dawson S, Donaghue KC, et al. ACE Inhibitors and Statins in Adolescents with Type 1 Diabetes. N Engl J Med. 2017;377(18):1733-45.

61. Knerr I, Dost A, Lepler R, Raile K, Schober E, Rascher W, et al. Tracking and prediction of arterial blood pressure from childhood to young adulthood in 868 patients with type 1 diabetes: a multicenter longitudinal survey in Germany and Austria. Diabetes Care. 2008;31(4):726-7.

62. Rodriguez BL, Dabelea D, Liese AD, Fujimoto W, Waitzfelder B, Liu L, et al. Prevalence and correlates of elevated blood pressure in youth with diabetes mellitus: the SEARCH for diabetes in youth study. J Pediatr. 2010;157(2):245-51.e1.

63. Shah RD, Braffett BH, Tryggestad JB, Hughan KS, Dhaliwal R, Nadeau KJ, et al. Cardiovascular risk factor progression in adolescents and young adults with youth-onset type 2 diabetes. J Diabetes Complications. 2022;36(3):108123.

64. Donaghue KC, Wadwa RP, Dimeglio LA, Wong TY, Chiarelli F, Marcovecchio ML, et al. ISPAD Clinical Practice Consensus Guidelines 2014. Microvascular and macrovascular complications in children and adolescents. Pediatr Diabetes. 2014;15 Suppl 20:257-69.

65. Canas JA, Ross JL, Taboada MV, Sikes KM, Damaso LC, Hossain J, et al. A randomized, double blind, placebo-controlled pilot trial of the safety and efficacy of atorvastatin in children with elevated low-density lipoprotein cholesterol (LDL-C) and type 1 diabetes. Pediatr Diabetes. 2015;16(2):79-89.

66. Downie E, Craig ME, Hing S, Cusumano J, Chan AK, Donaghue KC. Continued reduction in the prevalence of retinopathy in adolescents with type 1 diabetes: role of insulin therapy and glycemic control. Diabetes Care. 2011;34(11):2368-73.

67. Liu LL, Lawrence JM, Davis C, Liese AD, Pettitt DJ, Pihoker C, et al. Prevalence of overweight and obesity in youth with diabetes in USA: the SEARCH for Diabetes in Youth study. Pediatr Diabetes. 2010;11(1):4-11.

68. Valent D, Pestak K, Otis M, Shubrook J. Type 2 diabetes in the pediatric population: Are we meeting ADA clinical guidelines in Ohio? Clin Pediatr (Phila). 2010;49(4):316-22.

69. Conway B, Miller RG, Costacou T, Fried L, Kelsey S, Evans RW, et al. Adiposity and mortality in type 1 diabetes. Int J Obes (Lond). 2009;33(7):796-805.

70. Savva SC, Tornaritis M, Savva ME, Kourides Y, Panagi A, Silikiotou N, et al. Waist circumference and waist-to-height ratio are better predictors of cardiovascular disease risk factors in children than body mass index. Int J Obes Relat Metab Disord. 2000;24(11):1453-8.

71. Dalla Pozza R, Beyerlein A, Thilmany C, Weissenbacher C, Netz H, Schmidt H, et al. The effect of cardiovascular risk factors on the longitudinal evolution of the carotid intima medial thickness in children with type 1 diabetes mellitus. Cardiovasc Diabetol. 2011;10:53.

72. Bohn B, Herbst A, Pfeifer M, Krakow D, Zimny S, Kopp F, et al. Impact of Physical Activity on Glycemic Control and Prevalence of Cardiovascular Risk Factors in Adults With Type 1 Diabetes: A Cross-sectional Multicenter Study of 18,028 Patients. Diabetes Care. 2015;38(8):1536-43.

73. Quirk H, Blake H, Tennyson R, Randell TL, Glazebrook C. Physical activity interventions in children and young people with Type 1 diabetes mellitus: a systematic review with meta-analysis. Diabet Med. 2014;31(10):1163-73.

74. MacMillan F, Kirk A, Mutrie N, Matthews L, Robertson K, Saunders DH. A systematic review of physical activity and sedentary behavior intervention studies in youth with type 1 diabetes: study characteristics, intervention design, and efficacy. Pediatr Diabetes. 2014;15(3):175-89.

75. Eliasson B. Cigarette smoking and diabetes. Prog Cardiovasc Dis. 2003;45(5):405-13.

76. Houston TK, Person SD, Pletcher MJ, Liu K, Iribarren C, Kiefe CI. Active and passive smoking and development of glucose intolerance among young adults in a prospective cohort: CARDIA study. Bmj. 2006;332(7549):1064-9.

77. Schwab KO, Doerfer J, Hallermann K, Krebs A, Schorb E, Krebs K, et al. Marked smoking-associated increase of cardiovascular risk in childhood type 1 diabetes. Int J Adolesc Med Health. 2008;20(3):285-92.

78. Herbst A, Kordonouri O, Schwab KO, Schmidt F, Holl RW. Impact of physical activity on cardiovascular risk factors in children with type 1 diabetes: a multicenter study of 23,251 patients. Diabetes Care. 2007;30(8):2098-100.

79. Kim WY, Astrup AS, Stuber M, Tarnow L, Falk E, Botnar RM, et al. Subclinical coronary and aortic atherosclerosis detected by magnetic resonance imaging in type 1 diabetes with and without diabetic nephropathy. Circulation. 2007;115(2):228-35.

80. Soedamah-Muthu SS, Chaturvedi N, Witte DR, Stevens LK, Porta M, Fuller JH. Relationship between risk factors and mortality in type 1 diabetic patients in Europe: the EURODIAB Prospective Complications Study (PCS). Diabetes Care. 2008;31(7):1360-6.

81. Torffvit O, Lövestam-Adrian M, Agardh E, Agardh CD. Nephropathy, but not retinopathy, is associated with the development of heart disease in Type 1 diabetes: a 12-year observation study of 462 patients. Diabet Med. 2005;22(6):723-9.

82. de Boer IH, Katz R, Cao JJ, Fried LF, Kestenbaum B, Mukamal K, et al. Cystatin C, albuminuria, and mortality among older adults with diabetes. Diabetes Care. 2009;32(10):1833-8.

83. Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet. 2010;375(9731):2073-81.

84. de Boer IH, Sun W, Cleary PA, Lachin JM, Molitch ME, Steffes MW, et al. Intensive diabetes therapy and glomerular filtration rate in type 1 diabetes. N Engl J Med. 2011;365(25):2366-76.

85. Lemley KV. When to initiate ACEI/ARB therapy in patients with type 1 and 2 diabetes. Pediatr Nephrol. 2010;25(10):2021-34.

86. Lopes-Virella MF, Carter RE, Gilbert GE, Klein RL, Jaffa M, Jenkins AJ, et al. Risk factors related to inflammation and endothelial dysfunction in the DCCT/EDIC cohort and their relationship with nephropathy and macrovascular complications. Diabetes Care. 2008;31(10):2006-12.

87. Caramori ML, Rossing P. Diabetic Kidney Disease. In: Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E, et al., editors. Endotext. South Dartmouth (MA): MDText.com, Inc. Copyright © 2000-2024, MDText.com, Inc.; 2000.

88. Duell PB, Welty FK, Miller M, Chait A, Hammond G, Ahmad Z, et al. Nonalcoholic Fatty Liver Disease and Cardiovascular Risk: A Scientific Statement From the American Heart Association. Arterioscler Thromb Vasc Biol. 2022;42(6):e168-e85.

89. Bronner MB, Peeters MAC, Sattoe JNT, van Staa A. The impact of type 1 diabetes on young adults' health-related quality of life. Health Qual Life Outcomes. 2020;18(1):137.

90. Brinck J, Hagström E, Nåtman J, Franzén S, Eeg-Olofsson K, Nathanson D, et al. Cardiovascular Outcomes in Patients With Both Diabetes and Phenotypic Familial Hypercholesterolemia: A Nationwide Register-Based Cohort Study. Diabetes Care. 2022;45(12):3040-9.

91. Besseling J, Kastelein JJ, Defesche JC, Hutten BA, Hovingh GK. Association between familial hypercholesterolemia and prevalence of type 2 diabetes mellitus. Jama. 2015;313(10):1029-36.

92. Maurice-Stam H, Nijhof SL, Monninkhof AS, Heymans HSA, Grootenhuis MA. Review about the impact of growing up with a chronic disease showed delays achieving psychosocial milestones. Acta Paediatr. 2019;108(12):2157-69.

93. Monaghan M, Helgeson V, Wiebe D. Type 1 diabetes in young adulthood. Curr Diabetes Rev. 2015;11(4):239-50.

94. Nielsen HB, Ovesen LL, Mortensen LH, Lau CJ, Joensen LE. Type 1 diabetes, quality of life, occupational status and education level - A comparative population-based study. Diabetes Res Clin Pract. 2016;121:62-8.

95. Menting J, Tack CJ, Donders R, Knoop H. Potential mechanisms involved in the effect of cognitive behavioral therapy on fatigue severity in Type 1 diabetes. J Consult Clin Psychol. 2018;86(4):330-40.

96. Menting J, Tack CJ, van Bon AC, Jansen HJ, van den Bergh JP, Mol M, et al. Web-based cognitive behavioural therapy blended with face-to-face sessions for chronic fatigue in type 1 diabetes: a multicentre randomised controlled trial. Lancet Diabetes Endocrinol. 2017;5(6):448-56.

97. Ashraf AP, Sunil B, Bamba V, Breidbart E, Brar PC, Chung S, et al. Case Studies in Pediatric Lipid Disorders and Their Management. J Clin Endocrinol Metab. 2021;106(12):3605-20.

98. Hill-Briggs F, Fitzpatrick SL. Overview of Social Determinants of Health in the Development of Diabetes. Diabetes Care. 2023;46(9):1590-8.

99. Hill-Briggs F, Adler NE, Berkowitz SA, Chin MH, Gary-Webb TL, Navas-Acien A, et al. Social Determinants of Health and Diabetes: A Scientific Review. Diabetes Care. 2020;44(1):258-79.

100. Golden SH, Brown A, Cauley JA, Chin MH, Gary-Webb TL, Kim C, et al. Health disparities in endocrine disorders: biological, clinical, and nonclinical factors--an Endocrine Society scientific statement. J Clin Endocrinol Metab. 2012;97(9):E1579-639.

101. Suglia SF, Koenen KC, Boynton-Jarrett R, Chan PS, Clark CJ, Danese A, et al. Childhood and Adolescent Adversity and Cardiometabolic Outcomes: A Scientific Statement From the American Heart Association. Circulation. 2018;137(5):e15-e28.

102. Te Vazquez J, Feng SN, Orr CJ, Berkowitz SA. Food Insecurity and Cardiometabolic Conditions: a Review of Recent Research. Curr Nutr Rep. 2021;10(4):243-54.

103. Clemens KK, Le B, Anderson KK, Shariff SZ. Childhood food insecurity and incident diabetes: A longitudinal cohort study of 34 042 children in Ontario, Canada. Diabet Med. 2021;38(5):e14396.

104. Lee AM, Scharf RJ, Filipp SL, Gurka MJ, DeBoer MD. Food Insecurity Is Associated with Prediabetes Risk Among U.S. Adolescents, NHANES 2003-2014. Metab Syndr Relat Disord. 2019;17(7):347-54.

105. Fulay AP, Vercammen KA, Moran AJ, Rimm EB, Leung CW. Household and child food insecurity and CVD risk factors in lower-income adolescents aged 12-17 years from the National Health and Nutrition Examination Survey (NHANES) 2007-2016. Public Health Nutr. 2022;25(4):922-9.

106. Malik FS, Liese AD, Reboussin BA, Sauder KA, Frongillo EA, Lawrence JM, et al. Prevalence and Predictors of Household Food Insecurity and Supplemental Nutrition Assistance Program Use in Youth and Young Adults With Diabetes: The SEARCH for Diabetes in Youth Study. Diabetes Care. 2023;46(2):278-85.

107. Suglia SF, Campo RA, Brown AGM, Stoney C, Boyce CA, Appleton AA, et al. Social Determinants of Cardiovascular Health: Early Life Adversity as a Contributor to Disparities in Cardiovascular Diseases. J Pediatr. 2020;219:267-73.

108. 4. Comprehensive Medical Evaluation and Assessment of Comorbidities: Standards of Care in Diabetes-2024. Diabetes Care. 2024;47(Suppl 1):S52-s76.

109. Hussain T, Bagnall A, Agwu JC. NICE guidelines for hyperlipidaemia in children and young people with type I diabetes: time for a rethink? Arch Dis Child. 2006;91(6):545.

110. Waitzfelder B, Pihoker C, Klingensmith G, Case D, Anderson A, Bell RA, et al. Adherence to guidelines for youths with diabetes mellitus. Pediatrics. 2011;128(3):531-8.

111. Piona C, Chobot A, Dos Santos TJ, Giani E, Marcovecchio ML, Maffeis C, et al. Vascular complications in children and young people with type 1 diabetes: a worldwide assessment of diabetologists' adherence to international recommendations. Horm Res Paediatr. 2024.

112. Petitti DB, Imperatore G, Palla SL, Daniels SR, Dolan LM, Kershnar AK, et al. Serum lipids and glucose control: the SEARCH for Diabetes in Youth study. Arch Pediatr Adolesc Med. 2007;161(2):159-65.

113. Shah VN, Grimsmann JM, Foster NC, Dost A, Miller KM, Pavel M, et al. Undertreatment of cardiovascular risk factors in the type 1 diabetes exchange clinic network (United States) and the prospective diabetes follow-up (Germany/Austria) registries. Diabetes Obes Metab. 2020;22(9):1577-85.

114. Foster NC, Beck RW, Miller KM, Clements MA, Rickels MR, DiMeglio LA, et al. State of Type 1 Diabetes Management and Outcomes from the T1D Exchange in 2016-2018. Diabetes Technol Ther. 2019;21(2):66-72.

115. Miller KM, Foster NC, Beck RW, Bergenstal RM, DuBose SN, DiMeglio LA, et al. Current state of type 1 diabetes treatment in the U.S.: updated data from the T1D Exchange clinic registry. Diabetes Care. 2015;38(6):971-8.

116. Bjornstad P, Cree-Green M, Baumgartner A, Coe G, Reyes YG, Schäfer M, et al. Achieving ADA/ISPAD clinical guideline goals is associated with higher insulin sensitivity and cardiopulmonary fitness in adolescents with type 1 diabetes: Results from RESistance to InSulin in Type 1 ANd Type 2 diabetes (RESISTANT) and Effects of MEtformin on CardiovasculaR Function in AdoLescents with Type 1 Diabetes (EMERALD) Studies. Pediatr Diabetes. 2018;19(3):436-42.

117. Bjornstad P, Pyle L, Nguyen N, Snell-Bergeon JK, Bishop FK, Wadwa RP, et al. Achieving International Society for Pediatric and Adolescent Diabetes and American Diabetes Association clinical guidelines offers cardiorenal protection for youth with type 1 diabetes. Pediatr Diabetes. 2015;16(1):22-30.

118. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. Pediatrics. 2011;128 Suppl 5(Suppl 5):S213-56.

119. Daniels SR, Greer FR. Lipid screening and cardiovascular health in childhood. Pediatrics. 2008;122(1):198-208.

120. Donaghue KC, Chiarelli F, Trotta D, Allgrove J, Dahl-Jorgensen K. ISPAD Clinical Practice Consensus Guidelines 2006-2007. Microvascular and macrovascular complications. Pediatr Diabetes. 2007;8(3):163-70.

121. Kavey RE, Allada V, Daniels SR, Hayman LL, McCrindle BW, Newburger JW, et al. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association Expert Panel on Population and Prevention Science; the Councils on Cardiovascular Disease in the Young, Epidemiology and Prevention, Nutrition, Physical Activity and Metabolism, High Blood Pressure Research, Cardiovascular Nursing, and the Kidney in Heart Disease; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research: endorsed by the American Academy of Pediatrics. Circulation. 2006;114(24):2710-38.

122. Silverstein J, Klingensmith G, Copeland K, Plotnick L, Kaufman F, Laffel L, et al. Care of children and adolescents with type 1 diabetes: a statement of the American Diabetes Association. Diabetes Care. 2005;28(1):186-212.