

CARDIOVASCULAR RISK REDUCTION IN YOUTH WITH DIABETES- OPPORTUNITIES AND CHALLENGES

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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).

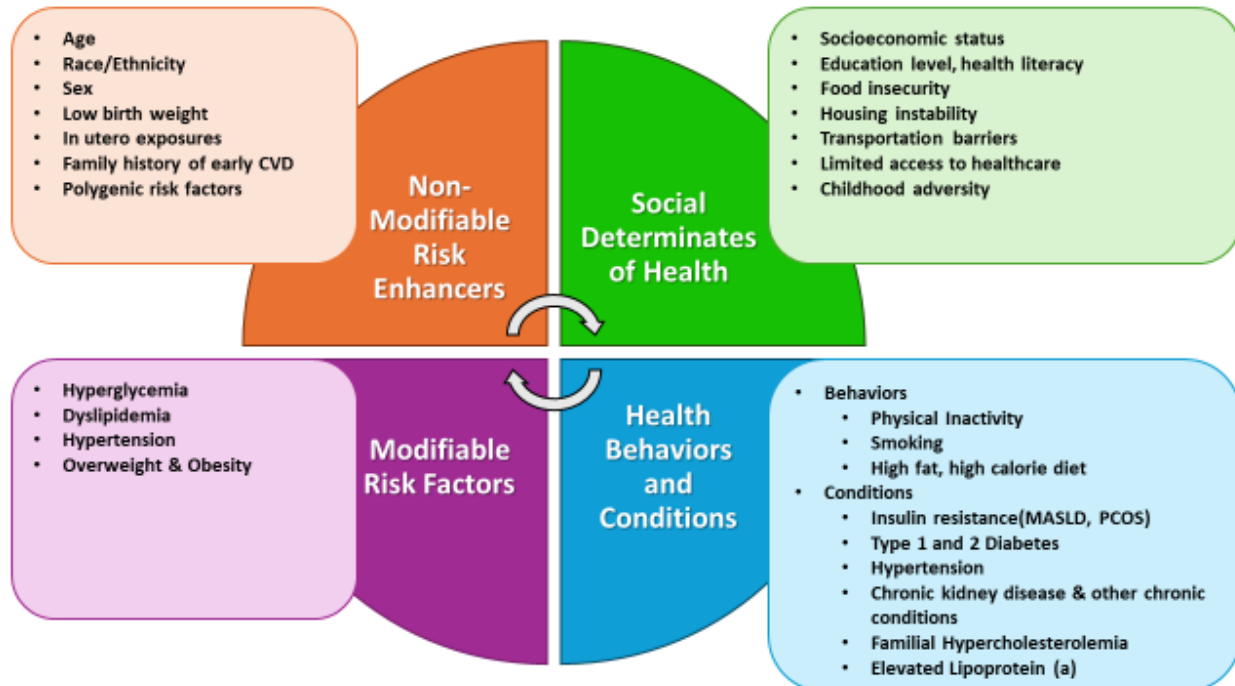


Figure 1. Global risk factors associated with cardiovascular disease. Adapted from (39).

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 months Automated insulin delivery systems may be considered to improve glycemic control.	Glycemic status should be assessed at least every 3 months Real-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	<p>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.</p> <p>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.</p>	<p>Initial lipid profile should be performed soon after diagnosis, preferably after glycemia has improved.</p> <p>If LDL-C values are within the accepted risk level (< 100 mg/dL [2.6 mmol/L]), a lipid profile repeated annually.</p>	<p>LDL-C value < 100 mg/dL (2.6 mmol/L).</p> <p>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 < 130 mg/dL</p>	<p>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.</p> <p>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</p>
Blood Pressure	BP should be measured at every routine visit.	Same as T1D	BP < 90 th percentile for age, sex, and height or, in adolescents aged ≥ 13 years, $< 130/80$ mmHg.	In youth with high BP (≥ 90 th percentile for age, sex, and height or, in adolescents aged ≥ 13 years, BP $\geq 120/80$ 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 at Endotext [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 $\leq 90^{\text{th}}$ 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 $> 95^{\text{th}}$ 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 $\sim 80\%$ among youth with T2D; $\sim 10\%$ being overweight (67). In the SEARCH for Diabetes in Youth study among children 3-19 years-of-age, the prevalence of a BMI $>85^{\text{th}}$ 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.

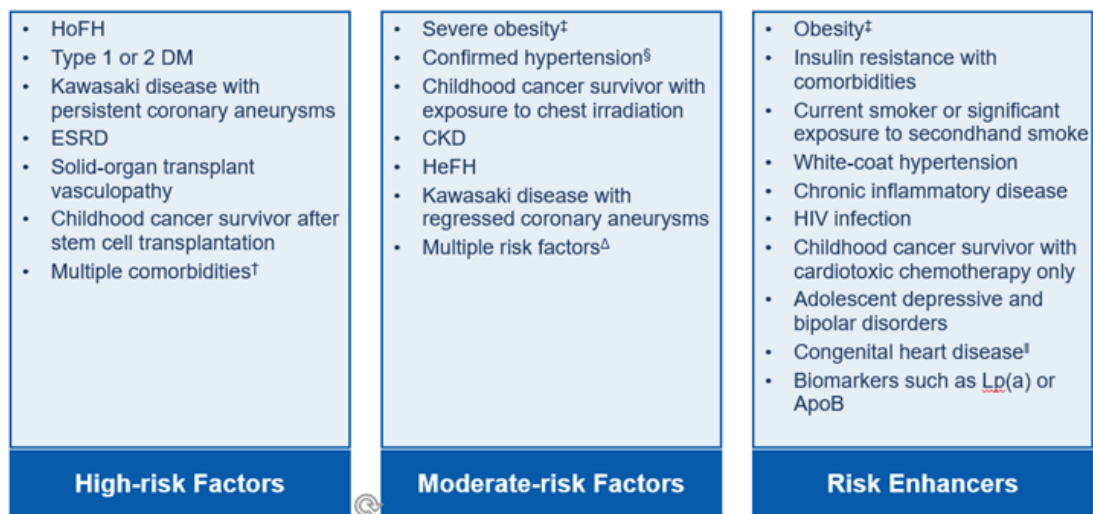


Figure 2. Health Conditions Associated With Increased Risk of CVD (97). †Any moderate-risk condition with ≥ 2 additional risk enhancers. ‡Severe obesity is defined as BMI ≥ 99 th percentile or ≥ 35 kg/m², and obesity is defined as BMI ≥ 95 th percentile to < 99 th percentile. §Defined as blood pressure > 95 th percentile or $\geq 130/80$ 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 (T1DX, 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	
<ul style="list-style-type: none"> • 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	
<ul style="list-style-type: none"> • 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	
<ul style="list-style-type: none"> • 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	
<ul style="list-style-type: none"> • 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.

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