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Macrovascular disease and risk factors in youth with type 1 diabetes: time to be more attentive to treatment?

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Summary (unstructured)

Cardiovascular disease (CVD) remains the leading etiology of mortality in type 1 diabetes (T1D). While CVD complications are rare until adulthood, pathology and early markers of CVD can manifest in adolescence. Whereas advances have been made in the management of microvascular complications of T1D, there is a lack of similar progress in reducing macrovascular complications. The reasons for the lack of progress remain incompletely understood. They likely relate to the longer time needed for CVD to manifest clinically and hence for risk factor management to show benefit, thus allowing inertia to prevail for diagnosis and particularly targeting of risk factors. In this review, we summarize the pediatric data on traditional and novel risk factors of CVD, provide an overview of previous and current clinical trials, discuss future directions in pediatric CVD research in T1D, and advocate for earlier identification and treatment of CVD risk factors as recommended in multiple guidelines.

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11. Contributors

PB, KCD and DMM researched the scientific literature and wrote the Review. PB, KCD and DMM made substantial contributions to the discussion of the content, and reviewed and edited the review before submission. PB prepared the figure and tables.

12. Declaration of interests

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1. Introduction

The overall global incidence of type 1 diabetes (T1D) is rising across the world with an especially concerning rate in children under the age of 5 years (1), translating to a lifetime of exposure and increased risk for early death from cardiovascular disease (CVD) (2–4). The strongest risk factors for CVD and mortality in T1D continue to be hyperglycemia, hypertension, dyslipidemia, diabetic kidney disease, insulin resistance and obesity (5–7). Whereas advances have been made in the management of microvascular complications of T1D (8) there is a lack of comparable progress in reduction of CVD (8). Current treatments, such as control of hyperglycemia and hypertension, are beneficial, but only partially protect against CVD. Furthermore, there are very few clinical trials in CVD prevention in youth---or adults---with T1D and therefore a lack of data on interventions to implement at an early stage of disease when pathology may be more responsive to therapy.

One limiting factor in reducing CVD is the delayed identification and treatment of these risk factors in youth with T1D. Data worldwide indicate that ADA/ISPAD goals for traditional CVD risk factor management are unmet despite these recommendations dating from 2006 (5, 6, 9–11). For example, in 2013 a substantial proportion of youth in the T1D Exchange Clinic Registry failed to meet the American Diabetes Association (ADA) and International Society for Pediatric and Adolescent Diabetes (ISPAD) targets for HbA1c (79%), systolic and diastolic blood pressure (SBP/DBP) [22%], LDL-cholesterol (LDL-C) [38%], triglycerides (TG) [11%] and body mass index (BMI) [31%] (12). Registry data also show low rates of treatment for hypertension, dyslipidemia and microalbuminuria in youth with T1D (13). We urge a call for action to promptly identify and treat these traditional CVD risk factors. Implementation of existing treatment guidelines, as well as identification of new modifiable risk factors and therapies, has the potential to reduce the 8–13-year gap in life expectancy in young people with T1D, much of which is attributable to CVD.

In this review, important pediatric data, ongoing trials, and recommendations on CVD screening and management in youth with T1D will be appraised. We will also discuss the research and clinical progress needed over the next 10 years to reduce morbidity and mortality from CVD in T1D.

2. What is the risk?

T1D is characterized by complications of the macro- (e.g. coronary artery disease [CAD]) and microvasculature (e.g. diabetic neuropathy, diabetic retinopathy and diabetic nephropathy [DN]) (14). CVD continues to be the leading cause of morbidity and mortality in T1D (15). CVD also disproportionally impacts women with T1D, which stands in contrast to the male predominance observed in the general population (16). T1D historically conferred a significant shortening of life expectancy (17). However, with the major advances in T1D treatment, recent epidemiologic data suggest that the mortality risk has been reduced (8, 18) (Supplemental Table 1). Despite this progress, other contemporary estimates of the burden of T1D on longevity suggest CVD is still a major cause of mortality and reduced life expectancy in T1D (3, 4, 19) (Supplemental Table 1). Furthermore, optimal glycemic control (HbA1c <7%) may not sufficiently abolish CVD risk in T1D (2, 20) (Supplemental Table 1).

In summary, recent epidemiologic data from Scotland and Australia suggest life span is 8–13 years (3, 4) shorter in people with T1D compared to their normoglycemic peers, which is primarily ascribed to CVD. Intensive glycemic control reduces, but does not abolish, CVD and mortality risk.

3. Risk factors

Traditional

The traditional CVD risk factors are hyperglycemia, hypertension, dyslipidemia and diabetic kidney disease (Supplemental Table 2). This review focuses on therapeutic inertia, and therefore summarizes modifiable rather than non-modifiable risk factors which are covered in other recent review and research papers (11, 21).

i. Hyperglycemia—While glycemic control remains the clinical cornerstone of CVD prevention in T1D, the data supporting the relationships between HbA1c and macrovascular complications are less convincing in T1D than for microvascular complications (11). Hyperglycemia likely contributes to CVD in T1D by several mechanisms, including promoting endothelial dysfunction and arterial stiffness (22, 23). Several adult studies support the association between hyperglycemia and CVD. Data on the association between glycemic control and CVD are weaker in pediatrics, as long-term studies in children with T1D are lacking and CVD events are typically absent until adulthood. Instead of hard CVD outcomes, pediatric studies rely on noninvasive imaging modalities to define early vascular changes (Supplemental Table 4). For example, in SEARCH CVD study, a relationship between worsening glycemic control and increased arterial stiffness was found (24, 25). In the same cohort, adjustments for glycemic control eliminated differences in cIMT between adolescents with T1D and non-diabetic controls, which may indicate a relationship between cIMT and HbA1c (26). In contrast to adult data, the relationship between HbA1c and measures of vascular health are mostly negative in pediatric studies (Supplemental Table 2). Therefore, longitudinal studies are needed in pediatrics to determine the effects of glycemic control on CVD outcomes, however these studies will require long follow-up as the relationship between HbA1c and CVD outcomes did not present clinically until 17 years of follow-up in the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC). Furthermore, a recent longitudinal analysis of the DCCT/EDIC study, found that the relationship between glycemic control and CVD outcomes are stable over time, whereas dyslipidemia and hypertension became progressively more important with aging and longstanding hyperglycemia (27). While one may argue that these data support concentrating on hyperglycemia in pediatric CVD risk reduction, it is important to appreciate that the relationships between hyperglycemia and dyslipidemia in youth with T1D is weak (28), and that hyperglycemia is not a determinant of insulin resistance with modern glycemic control or obesity in T1D (29).

ii. Hypoglycemia—Adult studies also implicate hypoglycemia as a risk factor for CVD and mortality. Pediatric studies are scarce, but one such study demonstrates that hypoglycemia and not glycemic variability or hyperglycemia relates to FMD in youth with T1D (30).

iii. Hypertension—Youth with T1D are disproportionally affected by hypertension compared to their normoglycemic peers. The prevalence of hypertension in youth with T1D is between 4–7%, which is higher than the 1–5% reported in youth without T1D (31). Risk factors for abnormal blood pressure patterns and hypertension in youth with T1D include obesity, autonomic dysfunction and hyperglycemia (32, 33). In adults with T1D the target blood pressures are defined as ≤130/80 mm Hg based on hard cardiovascular events in longitudinal studies (34). In the DCCT, a further reduction of blood pressure to <120/70 mm Hg carried substantially lower risk of adverse renal outcomes compared to ≤130/80 mm Hg (35). Whereas no longitudinal studies with hard cardiovascular outcomes exist in pediatric T1D, data suggest that target organ damage due to hypertension starts in youth (36) (Supplemental Table 2). In SEARCH CVD study, hypertension was linked to arterial stiffness and elevated cIMT (26). In addition, in a study with 24-hour ambulatory blood pressure monitoring found that loss of nighttime SBP dipping associated with cIMT (37). Accordingly, based on extrapolations from cross-sectional pediatric studies, and adult data, a target blood pressure ≤90th percentile for age, sex, and height is recommended by the ADA and ISPAD (38–40).

iv. Dyslipidemia—Youth with T1D have a high prevalence of dyslipidemia (41). In fact, the Diabetes-Patienten-Verlaufsdokumentation (DPV) registry reported hypercholesterolemia in 28.6% of participants (42). Similarly, persistently abnormal concentrations of total cholesterol, HDL-C and LDL-C were demonstrated over 10 years in US youth with T1D, with 28% and 11% with LDL-C concentrations ≥ 130 and 160 mg/dL respectively (43). Atherosclerosis starts early in life and relates to dyslipidemia (36, 44), which supports dyslipidemia as an important and potentially modifiable risk factor for CVD in youth with T1D (Supplemental Table 2). Autopsy studies such as the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Study found a relationship between arterial fatty streaks and dyslipidemia in youth (36), and the Bogalusa Heart Study found agreement between fatty streaks and LDL-C concentration. Furthermore, evidence of atherosclerosis was evident in children and adolescents (2 to 15 years of age) in up to 50% of cases in the Bogalusa Heart Study and that (44), although these were not T1D specific studies.

The Expert Panel on Blood Cholesterol Levels in Children and Adolescents categorizes dyslipidemia as total cholesterol >200 mg/dl (5.2 mmol/l), HDL-C <35 mg/dl (0.91 mmol/l), LDL-C >160 mg/dl (4.1 mmol/l), or TG >150 mg/dl (1.7 mmol/l) (45). The ISPAD and ADA recommends goals of: LDL-C < 100mg/dL; HDL-C > 35mg/dL; TG < 150mg/dL (38–40). The LDL-C goal <100mg/dl 2.6mmol /L) is further supported by data from the EDC study of adults with youth-onset T1D where a LDL-C above this threshold conferred increased risk of CVD (46).

v. Diabetic kidney disease—Diabetic kidney disease represents the major cause of end-stage renal disease and dialysis in the Western world, and is preceded by a long period without symptoms or signs of disease (47). In addition, diabetic kidney disease is increasingly recognized as a crucial risk factor for CVD (48, 49) and mortality (Supplemental Table 2). Elevated albumin excretion, previously termed microalbuminuria

and classically thought to be the earliest clinical marker of diabetic kidney disease, has a cumulative life-time incidence of almost 50% in T1D with an annual incidence rate of around 2 – 3 % (50). A recent report from the SEARCH for Diabetes in Youth Research Group demonstrated high prevalence of diabetic kidney disease (6%) along with arterial stiffness (11%) and hypertension (10%) in youth with T1D (51). Similarly, baseline data from The Adolescent Type 1 Diabetes Cardio-renal Intervention Trial (AdDIT) trial demonstrated higher arterial stiffness, defined as greater age and sex adjusted PWV, and greater aortic intima media thickness in adolescents with T1D with higher albumin excretion even within the normal range (52, 53). Findings from the T1D Exchange registry suggest under-treatment of elevated albumin excretion in youth with T1D with only 36% of participants with a clinical diagnosis of elevated albumin excretion received renin-angiotensin-aldosterone system inhibitors (13). Other important phenotypes of diabetic kidney disease include hyperfiltration, which is defined as glomerular filtration rate (GFR) greater than two standard deviations above the mean GFR for age and sex (54). Hyperfiltration is believed to represent the earliest intrarenal hemodynamic dysfunction in T1D (54), and along with rapid GFR decline are considered stronger predictors of nephropathy progression in T1D compared to elevated albumin excretion (47). Rapid GFR decline and impaired GFR are predictors of coronary artery calcification progression, a surrogate for CAD, in adults with T1D (49). While annual estimation of GFR is recommended by the ADA in youth with T1D, guidelines do not define hyperfiltration or rapid GFR decline, and do not incorporate changes in GFR in the treatment algorithms. Furthermore, current GFR estimation methods (based on serum creatinine and cystatin C) inaccurately and imprecisely ascertain GFR at the normal-to-elevated range (55).

Non-traditional

Non-traditional CVD risk factors include obesity, insulin resistance and lifestyle risk factors (Supplemental Table 3).

i. Obesity—Central adiposity is considered an important CVD risk factor that is augmented by intensive insulin therapy and is increasingly recognized in people with T1D (56). The incidence of obesity was recently reported to be 37% in one cohort of adults with newly diagnosed T1D (57), and 78% of men in the URO-EDIC study were overweight or obese (58). These data are not unique to North America, with similar prevalence and incidence observed in Australia (59), Israel (60) and Europe (61). Similar trends are seen in cohorts of youth with T1D as well (25, 62). In Australia, the BMI standard deviation scores (SDS) in youth with T1D increased from 0.47 SD to 0.82 SD over 10 years (63). In SEARCH, the prevalence of overweight in youth with T1D (age 3–19) was higher compared to their non-diabetic peers (22.1% *vs.* 16.1%) (62). Conversely, the Norwegian Study Group reported lower prevalence of obesity (4.4%), likely ascribed to the younger age, ethnicity and lifestyle differences (64). The rising prevalence of overweight and obesity in T1D likely reflects the trends in the general population, but may also relate to effects of improved glycemic control with intensive insulin regimens and fear of hypoglycemia leading to reduced exercise and increased carbohydrate intake (65). Irrespective of the contributory factors, the greater prevalence of overweight and obesity in youth with T1D (66) increases their lifetime risk for early death due to CVD (67) (Supplemental Table 3). Development of automated insulin

delivery (i.e. Artificial Pancreas [AP]) systems promises to improve glycemic control; however, it is uncertain whether this will be accompanied by increases in BMI and obesity as observed in the intensive arm of the DCCT (68) and how eating behaviors might change (69).

ii. Insulin Resistance—Insulin resistance is an established metabolic component of T1D (Supplemental Figure 1, Supplemental Table 3) that predicts incident CVD. Youth and adults with T1D are insulin resistant, even in comparison to normoglycemic peers of similar sexual maturation, body habitus, lipid levels and physical activity (56, 70). Furthermore, the insulin resistance is not a direct function of poor glycemic control, as contemporary cohorts demonstrate insulin resistance in lean youth with T1D despite modern advances in technology and better glycemic control (70). The mechanisms underlying the relationship between insulin resistance and the development and progression of CVD (48) in T1D while increasingly recognized, remains incompletely understood (Supplemental Table 3).

iii. Lifestyle risk factors—Lifestyle risk factors for CVD include exercise, diet, smoking and sleep, stress/depression (Supplemental Table 3). On average, youth with T1D are more sedentary and less fit compared to their nondiabetic peers (71). Physical activity was strongly associated with glycemic control in the DPV study (72). Furthermore, exercise capacity was linked with renal health (73) and insulin resistance (74), major determinants of CVD, in youth with T1D (74–77). The potential mechanisms whereby physical activity confers cardio-protection is summarized in Supplemental Figure 2. Regular exercise in youth with T1D can help achieve several CVD risk factor goals, including reducing HbA1c, triglycerides and total cholesterol (78).

While poor diet is an increasingly recognized risk factor for CVD (79) and medical nutrition therapy guidelines have demonstrated improvement in CVD risk factors in adults with T2D, studies examining the specific effect of dietary macronutrients have provided ambiguous results (80). Data to inform dietary guidelines specific for people with T1D to optimize glucose control, growth, healthy weight, and cardiovascular outcomes are needed.

Smoking is not a risk factor limited to adults with T1D, with 20% of youth with T1D in SEARCH reporting current smoking (81). In a study of youth with T1D in Egypt, 50% of the smokers demonstrated coronary artery calcification compared to only 9% of nonsmokers (82). The contribution of coronary artery calcification by cigarette smoking in youth with T1D is likely ascribed to worse glycemic and lipid control in addition to endothelial dysfunction (83).

Sleep is another important risk factor for CVD as alterations in sleep quantity or quality result in changes in appetite and satiety regulation, sympathetic nervous system activity (84) and metabolic dysfunction (84). As AP systems evolve they may improve sleep quality. Stress and depression are increasingly recognized contributors to poor glycemic control in T1D. Indeed, stressful life events in youth with T1D relate to worse glycemic control (85) and good family support may lower HbA1c among girls (85). Conversely, family stress may result in worse glycemic control, although this is likely bi-directional (86). General parental anxiety is linked to depressive symptoms and worse self-care and glycemic control (87)

whereas T1D-related stress in parents is conversely related to more frequent blood glucose monitoring and better self-care (87). Depression among youth with T1D is linked with worse glycemic control, in addition to increased prevalence of complications (88) which may be partially related to decreased blood glucose monitoring (89). Children and adolescents with any chronic illness including T1D are more afflicted by depression compared to the general population (90). In a large web-survey, 17% of youth with T1D reported symptoms of depression with only half of whom had discussed these concerns with their health care provider (91). While screening for depression is recommended in all youth (92), this is of paramount importance in those with T1D.

4. Current methods to evaluate CVD health in pediatrics

Accurate risk stratification of CVD in youth with T1D is required to implement successful prevention strategies. It is crucial to target youth with the highest risk for CVD using objective and noninvasive methods (Supplemental Table 3). One of the major difficulties in preventing CVD is attributed to the need to accurately target high risk patients at an early stage when disease may be most responsive to therapy. Accordingly, further development of techniques is needed to better target early changes in vascular function (e.g. arterial stiffness, dysfunctional vasodilation, arterial wall thickness and shear stress (Supplemental Table 4). Finally, it is important to underscore that there is a lack of long-term pediatric T1D studies demonstrating relationships between early markers of CVD and future CVD events.

i. Arterial stiffness—Measures of arterial stiffness are recognized as useful surrogate markers of atherosclerosis in youth (93). Compared to their non-diabetic counterparts, youth with T1D have increased arterial stiffness (94). Commonly used non-invasive methods to quantify arterial stiffness, including pulse wave velocity (PWV), augmentation index (AIx) and brachial distensibility (BrachD), are reported to predict future CVD events and all-cause mortality in adults (93) (Supplemental Table 4).

ii. Intima-media thickness—Atherosclerosis in youth can also be determined indirectly by arterial intima-media thickness (IMT), which is found to relate to CVD events in adults with T1D (95). Studies suggest that carotid IMT (cIMT) and aortic IMT (aIMT) are significantly higher in adolescents with T1D than their normoglycemic peers (96, 97), while others have not (98) (Supplemental Table 4). In the DCCT, adults in the intensive therapy arm experienced decreased progression of cIMT 6 years after trial completion (99).

iii. Vascular function—Ultrasound measurement of flow-mediated dilation (FMD) and glycerol trinitrate (GTN) induced dilation of the brachial artery are non-invasive techniques to assess endothelial and smooth muscle function. Youth with T1D demonstrate worse vascular function compared to normoglycemic peers (98).

iv. Cardiac and vascular magnetic resonance imaging (MRI)—Cardiac magnetic resonance imaging (CMR) has emerged as a promising non-invasive method to assess coronary artery disease, myocardial injury, aortic flow dynamics, cardiac function and structure (Supplemental Table 4). Central aortic stiffness is thought to be an early predictor of overt CVD in adults with T1D (100), yet data on children and adolescents are scarce.

Computational fluid dynamic modeling has been used to assess thoracic aortic wall properties, and has demonstrated reduced aortic distensibility and significantly elevated wall shear stress throughout the aorta in youth with T1D (101), but these findings need to be confirmed with phase-contrast MRI. Important limitations of CMR include cost and availability which will likely limit their application in clinical practice.

vi. Exercise testing—Cardiopulmonary fitness is decreased in T1D for reasons that are incompletely understood. Irrespective of the cause, low fitness in adults with and without T1D is an important determinant of CVD mortality and decreased longevity (102). Cardiopulmonary fitness can be measured by peak oxygen consumption during exercise testing (e.g. cycle ergometry) (Supplemental Table 4). Non-obese youth with T1D have reduced VO_2peak, compared to normoglycemic peers of similar sexual maturation, body habitus, and habitual level of physical activity (56). Interventions focused on improving cardiopulmonary fitness in T1D youth are needed.

5. Uptake of ADA and ISPAD treatment Goals

Collectively, elevated glucose, blood pressure and dyslipidemia are traditionally considered the major contributory factors for cardiovascular disease, but achieving these goals in children and adolescents remains difficult (5, 6, 9–11). Suboptimal ADA/ISPAD target achievement is associated with worse vascular health in youth with T1D as judged by surrogate markers of cardio-renal health, (Supplemental Table 2). The reasons for the suboptimal goal achievements are likely multifactorial. Compliance with Guidelines is more likely if the health care provider agrees with the Guideline (103) and more likely if the evidence is strong. Hence, reluctance or inertia in following existing guidelines may be due to the inferential nature of the evidence from adult studies. A logical question which remains unanswered is whether clinicians need further convincing about inferential data from which the treatment guidelines are derived. Or it could be due to pediatric provider unfamiliarity with these medications, recognized poor medication adherence and therefore reluctance to prescribe these medications during adolescence. All are potential causes. In addition, the physiologic insulin resistance of puberty exacerbated by rising rates of obesity in T1D and sedentary behavior among adolescents render this issue more urgent to address.

6. Clinical trial data and therapeutic inertia

While there have been few CVD clinical trials dedicated to youth with T1D, there are landmark studies worth highlighting. For example, the intensive glycemic control led to renal protection, a strong CVD risk factor, in 195 pubertal youth in the DCCT adolescent cohort (104). In the same cohort, the intensive treatment arm compared to the conventional therapy arm conferred reduced risk and progression of elevated albumin excretion by 54%. Furthermore, the beneficial effects of intensive therapy continued in the original adolescent cohort during the EDIC follow-up (105). Data from adolescents in the DCCT-EDIC on CVD outcomes requires longer follow-up.

Table 1 summarizes past clinical trials, and **Table 2** ongoing CVD therapy trials in adolescents and young adults with T1D. The Statins in Children with Type 1 Diabetes and

Hypercholesterolemia (NCT01236365) randomized placebo-controlled trial in 60 adolescents (mean age 15.0±0.3 years, 48% girls, mean T1D duration 6.8±0.5 years, mean LDL-C 124±4.0 mg/dl) demonstrated that 6 months of atorvastatin therapy lowered LDL-C, apoB and atherogenic lipoprotein subparticles in adolescents with T1D and elevated LDL-C (106). The AdDIT study, a randomized placebo-controlled trial in 443 adolescents (mean age of 12.4±1.4 years) with T1D with an ACE inhibitor (quinapril), a statin (atorvastatin), or the combination of the two, demonstrated that statins corrected lipid abnormalities and reduced hsCRP, although without short-term change in measures of CVD function. Similarly, ACE inhibition reduced ACR. Following standardized protocol both medications were safe in adolescents with T1D (106, 107). In other conditions of increased risk for CVD, the earlier the introduction of lipid lowering medication, the greater the benefit (108, 109). In fact, life-long small decreases in LDL-C in people with sequence variants in the proprotein convertase subtilisin/kexin type 9 serine protease gene (PCSK9) conferred substantial reductions in CVD events (109), and similar risk reduction may be observed when initiating LDL-C lowering therapies early in youth with T1D (Figure 1). Of note, the decrease in LDL-C with PCSK9 variants (a lifetime exposure) are similar to those from initial statin therapy (shorter term exposure), but the magnitude of CVD reduction was much greater with PCSK9 variants suggesting that earlier, low intensity treatment with a statin may result in a greater long-term reduction in CVD than later treatment when atherosclerosis has advanced.

The Metformin Therapy for Overweight Adolescents with Type 1 Diabetes study was a multicenter, double blind, placebo-controlled randomized control trial in 140 overweight and obese adolescents with T1D (mean age of 15.3 years with mean T1D duration of 7 years, 66% girls) (110). The participants were randomized to receive metformin versus placebo in addition to conventional insulin therapy, and at 6-month follow-up no differences in glycemic control were observed between the two groups (110).The metformin group had reduction in insulin dose and measures of adiposity (110). It is important to emphasize that this clinical trial was powered on HbA1c and not CVD end-points. A related study in youth with T1D demonstrated that 6-month metformin therapy reduced insulin resistance by hyperinsulinemic-euglycemic clamps, an important CVD risk factor (111). The REducing with MetfOrmin Vascular Adverse Lesions in Type 1 Diabetes (REMOVAL) study demonstrated in adults with T1D that 3 years of metformin therapy reduced maximal carotid intimal media thickness (cIMT), although progression of mean cIMT was not significantly reduced (112). Finally, the Does Metformin improve vascular function in youth with Type 1 Diabetes trial in Australia demonstrated improvement in vascular smooth muscle function with metformin in youth ages 8–18 years (113). There are many challenges encountered in designing clinical trials in youth with T1D. Some of the challenges are summarized in **Table 4** and include reliance on surrogate outcomes (soft outcomes) rather than event (hard outcomes), unreliable reference data for surrogate outcomes, and poor medical compliance in adolescence. Accordingly, strategies to address the therapeutic inertia include: 1) to improve the quality of evidence by using longitudinal registry data and combining multiple lines of evidence as surrogate markers are supportive and not definitive, 2) to enhance provider education, and 3) to encourage the use of benchmarking of therapies of CVD risk factors to improve quality of care. While improvements in the day-to-day use of research

results have been reported by the National Committee for Quality Assurance (114), medical providers are the key to address current therapeutic inertia. To address this obstacle, professional organizations must lead the efforts to realize the full public health benefits of research. To this end, professional societies must work together to reach consensus on the guidelines to minimize conflicting recommendations. The busy clinician may find difficulty allocating time for CVD risk management in part due to their lack of training and in part due to unwillingness of the adolescent to accept additional therapy. The therapeutic inertia may also be ascribed to an overly optimistic dependence on lifestyle modifications prior to starting pharmacotherapy, and waiting until better glycemic control is achieved prior to starting statins for elevated LDL-C, rather than targeting both lipid and glycemic control in parallel. While lifestyle modifications are important, both the clinician and patient should agree on a realistic timeframe, and commit to pharmacotherapy when these lifestyle changes fail. While certain studies suggest that macrovascular disease is rare in adults with T1D without evidence of diabetic kidney disease (7), misguided interpretation of such data may explain why clinicians are hesitant to start pharmacotherapy to reduce CVD risk in youth with T1D, most of whom are without clinical evidence of diabetic kidney disease. Especially since progression of atherosclerosis occurs in the absence of elevated albumin excretion (115). Unfamiliarity with recent treatment guidelines for hypertension and dyslipidemia may also deter pediatric diabetologists from starting pharmacotherapy. Investment in registries is needed to provide rich data sets to address research questions which may be too cumbersome or expensive to answer with randomized clinical trials. Benchmarking registries and quality improvement efforts are also required to better understand where to target interventions to improve quality of care. Finally, the investigators and sponsors should preferentially support research efforts that are amenable to clinical application.

7. Recommendations

Substantial gaps exist in our knowledge and understanding of the safety and efficacy of CVD therapies in children and adolescents with T1D. Accordingly, we have summarized some important unanswered research questions in **Table 3**. While results from observational studies in youth with T1D have identified several risk factors associated with surrogate markers of CVD, we need more randomized control trials in CVD in youth with T1D to evaluate whether these relationships are causal and how intervention will improve long-term outcomes. AdDIT is an example of a CVD trial in youth with T1D and its results demonstrate to clinicians the safety of statin and ACE treatment and their effectiveness in lowering LDL and ACR, but also highlight important challenges for the research community (116). Some of the challenges include: 1) rates of withdrawal and adherence: 18% and 70%; 2) increase in HbA1c during the study; 3) the need for multi-decade longitudinal follow-up to determine end-points such as cardiovascular events or death; 4) cost for such studies in an increasingly challenging research funding climate. Given the need for long term randomized clinical trials, it is likely that many of these research questions will remain unaddressed in the current funding environment. The best treatment decisions for youth with T1D will therefore continue to depend on a combination of several sources of data and inferences from adult studies. On the other hand, it is equally important to recognize that interventions

that failed to show benefit in adults with advanced CVD, may be beneficial in youth with early markers of CVD.

8. What progress do we need to make in the next 10 years?

Priorities to enhance cardiovascular health in children and adolescents with T1D are summarized in **Table 3**, and include a better differentiation of guidelines for youth with T1D vs. T2D. It is very likely that there are pathophysiological differences driving CVD risk in children and adolescents with T1D and T2D, and therefore disease-specific preventive strategies and therapies are warranted. There is also a need for more information on how well the surrogate markers predict CVD events, and whether newer methods to evaluate vascular health (e.g. speckle tracking and MRI-based methods) are superior markers of cardiovascular health, although these will remain research tools given costs. These data are needed to convince the clinical community to change guidelines and practice based on pediatric trials with surrogate markers as outcomes (117). Furthermore, mechanistic and experimental studies with hemodynamic outcomes are needed to define the pathophysiology of early CVD in youth with T1D. Randomized controlled trials evaluating therapies to impede development of CVD in youth with T1D are also needed. Clinical trial data will also direct the aptness of pharmacotherapy targeting CVD risk factors in youth. International and multicenter efforts with partnerships between governmental institutions, foundations and industry are required to make such studies feasible. AdDIT is an example of a multinational investigator led randomized clinical trial across 3 continents. An important clinical impact of AdDIT is the demonstration of safety and acceptance for ACEi and statin therapy in youth with T1D. Unfortunately, the primary endpoint of reduced albumin excretion was not met in adolescents identified to be in the high level of the normal range. The 43% hazard reduction of the cumulative incidence of microalbuminuria was not considered significant for a secondary outcome. Potential benefit for cIMT and other CVD risk markers may be uncovered during the planned follow-up (as occurred in the EDIC phase of the DCCT). Similarly, in youth with type 2 diabetes, studies such as TODAY implemented protocol driven pharmacologic treatment of elevated blood pressure and lipids which may increase awareness of the need to aggressively treat these CVD risk factors. To improve survival, we also need to reduce the time lag from research results and guidelines to clinical implementation. The combination of mechanistic studies and randomized clinical trials will allow the research community to set well-defined risk factor goals and improve our understanding of optimal treatment to prevent CVD events in youth with T1D.

9. Conclusion

In summary, it is well established that the atherosclerotic process starts in adolescence. Furthermore, adolescents with T1D have an elevated risk of CVD which continues to be the principal cause of mortality in T1D and an important contributor to the reported 8–13 year decrease in life-span in T1D. Early intervention can have the greatest effect on prevention and data from the AdDIT study demonstrate safety and short-term LDL-C, BP and ACR improvements with statin and ACEi treatment, in addition to the need for better glucose control and optimizing healthy lifestyle. Therefore, we propose that earlier, treatment of CVD risk factors such as dyslipidemia and hypertension will have long-term benefit at low

risk and cost and should be more widely used in pediatric T1D care. Efforts to improve future CVD outcomes and mortality in T1D should start in adolescence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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10. Search strategy and selection criteria

We searched PubMed and Medline for English language abstracts and full-text articles on cardiovascular disease in youth with T1D. The keywords used to search included: “cardiovascular disease”, “type 1 diabetes”, “risk factors”, “adolescents”, “diabetic kidney disease”, “clinical trials”, “arterial stiffness”, “obesity”, “smoking”, “lifestyle changes”, “insulin resistance”, “insulin sensitivity”, “metformin”, “statins”, “ACE inhibitors”, “hypertension”, “hyperglycemia”, “dyslipidemia”, “ISPAD”, “ADA”, “family history”, “insulin”. The keywords were used as individual search terms and in combinations. In addition, we searched ClinicalTrial.gov, Clinicaltrialsregister.eu and Anzctr.org.au for pediatric T1D clinical trials with similar search words. Finally, we reviewed bibliography of original articles, narrative reviews, clinical guidelines, and previous systematic reviews and meta-analyses for further relevant reference material.

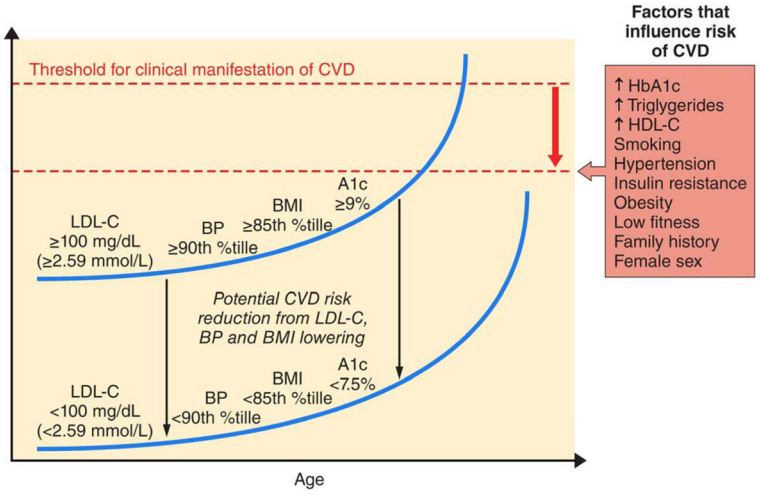

Figure 1. Possible Long-term CVD Risk Reduction from Risk Factor Control

Figure 1 represents potential long-term risk reduction assuming high benefit from risk factor (LDL-C, BP, BMI and A1c) lowering, and greater risk reduction when therapy initiated at an earlier age / shorter T1D duration. Individual threshold for clinical CVD (represented by the red dotted horizontal lines) can be raised or lowered depending on risk factor profiles.

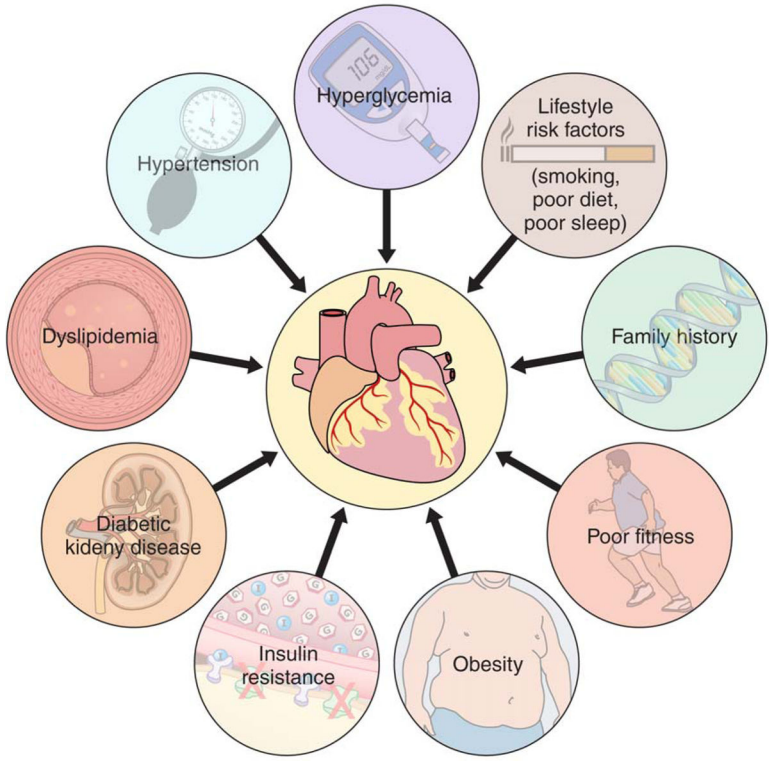

Figure 2.
Cardiovascular Risk Factors in Youth with T1D