Type 1 Diabetes and Cardiovascular Health

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KEYWORDS

• Type 1 diabetes • Cardiovascular health • Cardiovascular disease risk • Prevention

KEY POINTS

- Type 1 diabetes (T1D) is associated with an increased risk of cardiovascular disease (CVD), which is higher in those diagnosed at early age and with longer disease duration.
- Glycemia is the strongest modifiable risk factor for CVD, although traditional CVD risk factors are involved as well.
- There is an undertreatment of CVD risk factors in T1D, particularly in young adults.
- To promote cardiovascular health (CVH) in T1D, the eight CVH metrics proposed for the general population should adopt targets specific for the T1D population.

INTRODUCTION

In 2010, the American Health Association introduced the concept of cardiovascular health (CVH).[1] The definition was updated in 2022 and now includes four health behaviors and four health factors which, when optimal, are associated with increased longevity and better quality of life.[2] Ideal CVH is defined by the presence of health behaviors such as DASH- and Mediterranean-style eating patterns, physical activity $\geq$150 min/week of moderate-(or greater) intensity activity, never smoking, sleeping 7 -< 9 hours per night, and health factors such as a body mass index (BMI) less than 25 kg/m^2, non-high-density lipoprotein (HDL) cholesterol less than 130 mg/dL, fasting blood glucose less than 100 mg/dL or glycated hemoglobin test (HbA1c) less than 5.7%, and blood pressure less than 120/80 mm Hg[2]. Currently, there are no specific recommendations about the use of these metrics in type 1 diabetes (T1D) management. To address this, a comprehensive approach to CVH in T1D is needed, which requires understanding the impact of the disease on the occurrence

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of CVD, identifying cardiovascular disease (CVD) risk factors and T1D individuals who are at increased risk, and identifying CVH treatment targets and approaches/implementation strategies to reach these goals.

EPIDEMIOLOGY OF CARDIOVASCULAR DISEASE IN TYPE 1 DIABETES

Mortality rates for people with T1D vary by geographic location but are 3 to 18 times higher than what would be expected in their respective countries.[3] CVD is the leading cause of death, although renal disease is another contributor factor.[3] Although few studies have directly compared CVD mortality in people with T1D and people with type 2 diabetes (T2D), T1D seems to have an impact on mortality which is at least comparable if not higher than T2D.[4,5]

A meta-analysis which included 10 observational studies involving 166,027 patients with T1D and controls from the general population has shown that for people with T1D, the relative risk of coronary artery disease (CAD) is 9.38 (95% CI, 5.56–15.82), and of myocardial infarction is 6.37 (95% CI, 3.81–10.66).[6] In the European Diabetes Prospective Complication Study which analyzed a cohort of 3250 individuals with T1D, the incidence of a cerebrovascular accident was 0.74% per year, almost double of what is reported in the general population which is reported at 0.2% to 0.3% per year.[7] This finding was also supported by Nurses' Health Study.[8] Data about peripheral artery disease (PAD) are mostly derived from studies which focused on amputation. People with T1D have a rate of nontraumatic amputation of 0.4% to 7.2% per year.[9] In a meta-analysis of five studies of people with T1D, each 1% increase in mean HbA1c was associated with an 18% increased risk of PAD.[10]

RISK FACTORS FOR CARDIOVASCULAR DISEASE IN TYPE 1 DIABETES

Several factors increase the risk of CVD in T1D. They are listed in **Box 1** and the most relevant discussed below.

Glycemic Control

Hyperglycemia is a recognized risk factor for the development of both microvascular and macrovascular complications.[11] Hyperglycemia is associated with preclinical atherosclerosis as shown in the Oslo study where a 1% increase in mean HbA1c was associated with a 6.4% increase in coronary vessel stenosis.[12] In the Pittsburgh

Box 1
Factors associated with increased risk of cardiovascular disease in type 1 diabetes

Traditional risk factors
- Poor glycemic control
- Dyslipidemia
- High blood pressure
- Diabetic kidney disease
- Obesity
- Smoking

Additional risk factors
- Genetics
- Age of T1D onset
- Female sex
- Cardiac autonomic neuropathy
- Cardiac autoimmunity

Epidemiology of Diabetes Complications (EDC) study for every 1% increase in mean HbA1c, the risk of CVD over 25 years after adjusting for risk factors was increased between 1.13- and 1.26-fold.[13] In the EDC study and Diabetes Control and Complications Trial and follow-up Epidemiology of Diabetes Interventions and Complications study (DCCT/EDIC), HbA1c was the strongest risk factor for the first and subsequent CVD event.[11] Hyperglycemia however is not the only determinant of CVD risk in T1D because additional analyses have revealed that other risk factors such as systolic blood pressure and lipids attenuated up to ~50% the effect of glycemia on the risk of CVD in the DCCT/EDIC study.[14,15] Besides hyperglycemia, there is also some evidence that glycemic variability including hypoglycemia can contribute to future CVD events.[16–18]

Dyslipidemia

Poor glycemic control is associated with hypertriglyceridemia, elevated low-density lipoprotein cholesterol (LDL-C), and lower HDL cholesterol (HDL-C).[19] Data from the Swedish National Registry suggest that LDL-C is a significant predictor of CVD and mortality in T1D, with each 1 mmol/L (38.7 mg/dL) increase in LDL-C associated with 35% to 50% greater risk.[20] An association between LDL-C and CVD in people with T1D has been also reported in studies such as the DCCT/EDIC study and the EDC study.[21,22] In addition, in people with T1D, small dense LDL-C particle size is associated with CVD risk and dysfunctional HDL particles which may become proatherogenic have been reported.[23,24]

High Blood Pressure

Hypertension is a risk factor for CVD in the general population and people with T1D in the DCCT/EDIC study and EDC study.[21,22,25] Hypertension can be a consequence of diabetic kidney disease, but T1D is associated with higher prevalence of hypertension, also in the absence of diabetic kidney disease being three times more common in people with T1D compared with the nondiabetic population.[26]

Diabetic Kidney Disease

Several studies indicate that the diabetic kidney defined as the presence of albuminuria and/or reduced glomerular filtration rate is associated with an increased CVD risk in people with T1D.[22,27,28] The risk of all-cause mortality also increases with the severity of chronic kidney disease.[29] In addition, the Coronary Artery Calcification in Type 1 Diabetes (CACTI) study showed that an increasing albumin excretion and declining glomerular filtration rate predicted the progression of coronary artery calcification in 1066 participants with T1D compared with nondiabetic adults.[30]

Obesity

There is an increasing prevalence of overweight and obesity in people with T1D as shown by the DCCT/EDIC study where the prevalence of obesity increased from 1% of subjects at baseline to 31% after 12 years of follow-up in 2005.[31] This finding is comparable to the one of the EDC study and more recently the T1D Exchange Clinic Network.[32,33] The association of T1D with obesity and comorbidities such as hypertension and dyslipidemia has led to the definition of “double diabetes” to indicate people with T1D and with features of T2D, a condition which increases the CVD risk.[34]

Genetics

A major candidate gene for CVD risk in T1D is the haptoglobin (Hp), an acute phase protein with anti-oxidative properties. Hp is polymorphic with two major alleles and three genotypes.[35] The Hp 2-2 genotype has been associated with the occurrence

of CAD in the DCCT/EDIC study.[36,37] However, the Hp 2-2 genotype has not been identified by genome-wide association studies which instead found associations between increased CVD risk in T1D and single nucleotide polymorphisms, which, however, were weak or not replicated.[38,39]

Age of Type 1 Diabetes Onset

CVD occurs much earlier in people with T1D than in the general population, and premature atherosclerosis may be present in 50% to 70% of individuals by age 45 years.[40–42] In the Swedish National Diabetes registry which included 27,195 people with T1D, those with the disease onset before 10 years of age experienced a 30-fold increased risk of CAD and acute myocardial infarction compared with general population and had increased CVD mortality compared with those who were diagnosed between 26 and 30 years of age after adjusting for diabetes duration.[40]

Female Sex

Women with T1D have a higher risk for CVD than men.[40,41] In the general population, the rates of CAD in premenopausal women are lower than men, but in women with T1D age less than 40 years, the CVD rates are equal in both sex.[43–45] The reasons for these differences are unclear but may be secondary to the undertreatment of risk factors, different fat distribution, and different lipoprotein profiles. Nondiabetic women have a more favorable lipid profile than nondiabetic men, but women with T1D have concentration of LDL-C particles similar to men with T1D.[46–49]

PREDICTION OF CARDIOVASCULAR DISEASE IN TYPE 1 DIABETES

Different approaches have been used to identify people who are at an increased risk of CVD disease and to detect early signs of CVD.

Risk Predication Models

CVD risk calculators are available for the general population and people with T2D, but both the Framingham Risk Score and UK Prospective Diabetes Study (UKPDS) Risk Engine underestimate the CVD risk in T1D.[50] Models which have been developed to address the CVD risk in T1D include the Swedish National Diabetes Register (NDR), the Pittsburgh CHD in Type 1 Diabetes Risk Model, the Steno Type 1 Risk Engine, and the QRISK model.[51–54] Among these models, the Danish Steno Type 1 Risk Engine was externally validated and was superior to the NDR and UKPDS models in predicting the 5-year risk of first fatal or non-fatal CVD event in people with T1D.[53] The British QRISK latest version QRISK3, which accounts for the T1D or T2D status, predicts the 10-year CVD risk with a performance which is higher for people with T1D than T2D.[55] However, CVD risk prediction models for T1D are not widely adopted or recommended by guideline because of lack of international validation.[56]

Imaging to Detect Cardiovascular Disease

Imaging-based tests have been used to detect early signs of CVD.

- Diastolic dysfunction has been reported in adolescents, younger, and older adults with T1D.[57,58] Subclinical systolic dysfunction, which manifests subsequently, can occur in people with T1D but may not be detected by assessing the ejection fraction, which can be normal in the early stages of the disease.[59] Tissue Doppler imaging, speckle tracking echocardiography, and cardiac MRI can be used as screening methods but their use to predict CVD events has not been validated yet.[59–61]

- Arterial stiffness has been described in people with T1D. In particular, aortic stiffness has been identified as an independent maker of all-cause mortality in this population and can be assessed by carotid-femoral pulse wave velocity.[62,63]
- Carotid intima-media thickness (CIMT) is a surrogate marker of CVD disease. However, the DCCT/EDIC study failed to find a significant association between CIMT and subsequent coronary events after adjusting for traditional CVD risk factors.[64]
- Coronary Artery Calcium (CAC) test. Computed tomography is used to measure CAC in the four major coronary arteries. The Multi-Ethnic Study of Atherosclerosis cohort study has demonstrated that the CAC score has a prognostic value in determining the CVD risk in people with T2D.[65] In people with T1D in the EDC study, a score greater than 400 Agatston was the most efficient coronary calcium correlate of CAD.[66] More recent data from the DCCT/EDIC study found that a CAC score greater than 100 Agatston units was significantly associated with an increased risk of the subsequent occurrence of CVD and major cardiovascular events.[67] CAC score could detect asymptomatic atherosclerotic disease in T1D and in the clinical practice favor an aggressive therapy to reduce LDL-C to change the natural course of CVD.[68]

CARDIOVASCULAR DISEASE PREVENTION IN TYPE 1 DIABETES

No randomized trials have been specifically designed to assess the impact of CVD risk reduction strategies in T1D. Recommendations for the reduction of CVD risk in T1D are then mostly derived from data obtained from studies conducted in patients with T2D.

- The DCCT/EDIC study showed that hyperglycemia is modifiable risk factor for CVD in T1D.[69,70] The intensive glycemic control over a mean 6.5 years resulting in a mean HbA1c of 7.2% compared with 9.1% in the conventional therapy group determined a reduction of CVD which persisted beyond the completion of the intervention trial and despite the initial difference in glycemic control was not maintained on follow-up. During the 30 years of follow-up, the incidence of CVD in the former intensive treatment group decreased by 30% and the incidence of major cardiovascular events such as nonfatal myocardial infarction, stroke, or cardiovascular dearth by 32% compared with the former conventional therapy group.[70] Additional analyses have revealed that other risk factors such as systolic blood pressure and lipids attenuated up to ~50% of the effect of glycemia on the risk of CVD, but the association between HbA1c and the risk of CVD remained highly significant even after adjustment for these risk factors.[14,15] Maintaining an optimal glycemic control is then necessary to reduce the risk of CVD. Targeting HbA1c less than 7% or lower if this is not associated with hypoglycemia or adverse effects, or a time in range of 70 to 180 mg/dL greater than 70% is therefore recommended for most people with T1D.[71]
- Some trials investigating the effect of statin therapy in people with T2D have also included people with T1D. A meta-analysis, which included 18,686 people with diabetes from 14 randomized trials of statin therapy, inclusive of 17,220 participants with T2D and 1466 with T1D, has shown a 9% proportional reduction in all-cause mortality and 21% reduction in major vascular events, defined as the composite outcome of myocardial infarction or coronary death, stroke, or coronary revascularization, for each 1 mmol/L (39 mg/dL) reduction in LDL-C.[72] The evidence of benefit in adults with T1D was limited but not different from what

observed in patients with T2D. Recommendations for starting statin treatment for primary prevention in people with T1D are present in different guidelines.[73–75]

- In the EDC study, 605 participants with T1D without known CVD at baseline and followed for 25 years, the optimal blood pressure threshold associated with minimal CVD risk was 120/80 mm Hg.[73,76,77] People with T1D and hypertension should be treated with antihypertensive medications if the blood pressure is persistently above 130/80. The initial treatment can include any of the drug classes demonstrated to reduce CVD in people with diabetes: angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, thiazide-like diuretics, or dihydropyridine calcium channel blockers.
- Strategies for weight reduction can include medical nutrition therapy, physical activity, behavioral counseling, pharmacologic therapy, and bariatric surgery. People with T1D may benefit from eating plans that result in an energy deficit and that are lower in carbohydrate and glycemic index and higher in fiber and lean protein.[78] Mediterranean, DASH, vegetarian, or plant-based eating patterns have been shown to be beneficial in T2D, but there is limited evidence to support one specific eating pattern in T1D.[79] Physical activity is associated with weight loss, improved metabolic profile, and reduced CVD mortality in people with T1D.[80,81] The use of adjunct therapies, including glucagon-like peptide-1 analogs in particular, has been associated with weight loss and improved glycemic control but more studies are needed.[82] It is unclear at this time if bariatric surgery and weight loss medications in people with T1D are associated with improved glycemic control or reduced CVD risk.[83]
- Individuals with T1D should engage in 150 minute or more or moderate to vigorous intensity aerobic activity per week and in two to three sessions per week of resistance exercise on nonconsecutive days noting that blood glucose responses to physical activity in T1D are highly variable.[84,85]
- People with T1D should not use cigarettes, other tobacco products and e-cigarettes.[79]

CARDIOVASCULAR HEALTH IN TYPE 1 DIABETES

Better CVH scores are associated with lower risks of CVD disease.[86] CVH metrics can then be applied to people with T1D, but current CVH targets which are recommended for the general population should be modified to reflect the characteristics of T1D and goals associated with lower CVD risk in this population. For example, the measure for blood glucose should the HbA1c less than 7% or lower if this is not associated with hypoglycemia or adverse effect. Ideal blood lipids should be based on LDL-C and reflect the duration of disease and presence of additional risk factors. **Table 1** lists the ideal health behaviors and factors for CVH in adults with T1D.

CONSIDERATIONS

As the incidence of T1D in increasing worldwide and with the constant improvement in medical care and diabetes technology, the expectation is an increased number of older adults living with T1D who were diagnosed when they were children. Data from international registries such as the Type 1 Diabetes Exchange registry in United States and the German/Austrian diabetes-patienten-verlaufsdokumentation (DPV) Registry revealed that less than 40% of people with T1D reached HbA1c, blood pressure, and lipid goals.[87] In addition, more than 80% of young adults aged less than 26 years were not receiving antihypertensive or lipid-lowering medications despite

Table 1
Cardiovascular health goals for adults with type 1 diabetes

Domain	CVH Metric	Quantification
Health behaviors	Diet	Mediterranean-, DASH-style
	Physical activity	≥ 150 min/wk
	Nicotine exposure	Never/quit
	Sleep health	7-<9 h per night
Health factors	BMI	<25 Kg/m^2
	Blood lipids (76)	• LDL-C <100 mg/dL, if age <35 years or T1D duration <10 years • LDL-C <70 mg/dL and LDL-C reduction ≥50%, if T1D duration ≥10 years or another additional risk factor • LDL-C< 55 mg/dL and LDL-C reduction ≥50%, if T1D duration >20 years or target organ damage or ≥3 risk factors
	Blood glucose	HbA1c <7%, time in range 70–180 mg/dL >70%; target can be individualized
	Blood pressure	<120/80 mg/dL; if treated <130/80 mg/dL

Adapted from Lloyd-Jones DM, Allen NB, Anderson CAM, et al. Life's Essential 8: Updating and Enhancing the American Heart Association's Construct of Cardiovascular Health: A Presidential Advisory From the American Heart Association. Circulation 2022;146(5):e18-e43.

meeting criteria.[87] The presence of guidelines with different recommendations particularly in younger age groups is another factor which can contribute to different management and clinical inertia for younger people with T1D.[87,88] Strategies to improve CVH should then involve more education for both health care providers and people with diabetes. The development and distribution of educational tools could improve patients' health literacy. An alignment of the different guidelines can also help providers to better navigate the complex process of treatment decision-making. Finally, there is a need to reduce health inequities because with the recent advancements in diabetes technology, health care disparities in T1D treatment have also become more evident.[89]

SUMMARY

As the incidence of T1D in increasing worldwide and with improvements in medical care and diabetes technology, there is an increasing number of people with T1D at risk of CVD. Several CVD risk factors have been identified and therapeutic targets established to promote CVH in T1D. Tools such as risk prediction models and imaging-based tests have not been well validated in T1D, but the CAC test could detect asymptomatic atherosclerotic disease. CVD risk factors are also undertreated. Increased awareness about CVD risk in T1D for both health care providers and individuals with T1D and harmonization of different guidelines are recommended.

CLINICS CARE POINTS

- Discuss with people with type 1 diabetes (T1D) the increased risk of cardiovascular disease (CVD).
- Routinely address CVD risk factors such as elevated blood pressure and lipids in addition to glycemic control.

- Consider the Coronary Artery Calcium (CAC) screening test for better CVD risk stratification.
- Consider early treatment of CVD risk factors, in particular in young adults and women age less than 40 years.

DISCLOSURE

No competing financial interests exist.

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