Type 1 Diabetes Mellitus and Cardiovascular Disease: A Scientific Statement From the American Heart Association and American Diabetes Association

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SCIENTIFIC STATEMENT

Despite the known higher risk of cardiovascular disease (CVD) in individuals with type 1 diabetes mellitus (T1DM), the pathophysiology underlying the relationship between cardiovascular events, CVD risk factors, and T1DM is not well understood. Management approaches to CVD reduction have been extrapolated in large part from experience in type 2 diabetes mellitus (T2DM), despite the longer duration of disease in T1DM than in T2DM and the important differences in the underlying pathophysiology. Furthermore, the phenotype of T1DM is changing. As a result of the findings of the Diabetes Control and Complications Trial (DCCT), which compared intensive glycemic control with usual care, and its follow-up observational study, Epidemiology of Diabetes Interventions and Complications (EDIC), intensive management of diabetes mellitus (DM) has become the standard of care and has led to increasing longevity. However, our understanding of CVD in T1DM comes in large part from the previous era of less intensive glycemic control. More intensive glycemic control is associated with significant risk of weight gain, which may be magnified by the obesity epidemic. There is growing interest in better understanding the adverse effects of glycemia, the prevalence and type of lipid abnormalities in T1DM, the prognostic role of albuminuria and renal insufficiency, and the role of blood pressure (BP) in CVD. Obesity-associated metabolic abnormalities such as the proinflammatory state likely modify CVD risk in T1DM; however, the effect may be different from what is seen in T2DM. These concepts, and how they may affect management, have not been fully explored.

The present review will focus on the importance of CVD in patients with T1DM. We will summarize recent observations of potential differences in the pathophysiology of T1DM compared with T2DM, particularly with regard to atherosclerosis. We will explore the implications of these concepts for treatment of CVD risk factors in patients with T1DM. The relationship between CVD and other forms of DM will not be addressed in the present statement. The statement will identify gaps in knowledge about T1DM and CVD and will conclude with a summary of areas in which research is needed.

T1DM: DEFINITION AND DIAGNOSIS

T1DM is characterized by an absolute insulin deficiency caused by T-cell–mediated autoimmune destruction of pancreatic β-cells (1). It is the predominant form of DM during childhood and adolescence but can present in adulthood, with the typical symptoms of polyuria, polydipsia, and weight loss. The key pathophysiology is decreased insulin secretory capacity, which results in hyperglycemia with a propensity to develop ketoacidosis. The onset of T1DM frequently occurs in the setting of an intercurrent illness, which gives rise to the suspicion that its onset may be triggered by an infection. T1DM has strong human leukocyte antigen associations to the DQA, DQB, and DRB alleles (2). One or more autoantibodies, including islet cell, insulin, glutamic acid decarboxylase 65 (GAD65), zinc transporter 8 (3), and tyrosine phosphatase IA-2β and IA-2β antibodies, can be detected in 85–90% of individuals on presentation. The rate of β-cell destruction varies, generally occurring more rapidly

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at younger ages. However, T1DM can also present in adults, some of whom can have enough residual β-cell function to avoid dependence on insulin until many years later. When autoantibodies are present, this is referred to as latent autoimmune diabetes of adulthood. Infrequently, T1DM can present without evidence of autoimmunity but with intermittent episodes of ketoacidosis; between episodes, the need for insulin treatment can come and go. This type of DM, called idiopathic diabetes (1) or T1DM type B, occurs more often in those of African and Asian ancestry (4). Because of the increasing prevalence of obesity in the United States, there are also obese individuals with T1DM, particularly children. Evidence of insulin resistance (such as acanthosis nigricans); fasting insulin, glucose, and C-peptide levels; and the presence of islet cell, insulin, glutamic acid decarboxylase, and phosphatase autoantibodies can help differentiate between T1DM and T2DM, although both insulin resistance and insulin insufficiency can be present in the same patient (5), and rarely, T2DM can present at an advanced stage with low C-peptide levels and minimal islet cell function.

EPIDEMIOLOGY OF CVD IN PATIENTS WITH T1DM

Incidence and Prevalence of CVD

CVD is a long-term complication of T1DM that is a major concern for patients and healthcare providers. For the purposes of the present review, CVD will be defined as coronary heart disease (CHD), cerebrovascular disease, or peripheral artery disease (PAD). Heart failure and cardiomyopathy have also been described in T1DM (6,7), although information about these conditions in T1DM is less robust than for CHD and cerebrovascular disease, and they are not the focus of this review. CVD complications of T1DM include all of the above and probably represent different pathophysiological pathways. Abundant data are available from population studies and randomized trials regarding the incremental CVD risk associated with DM; however, the vast majority of these data derive either from cohorts of T2DM patients exclusively or more commonly from analyses of all DM patients without distinction as to type. In this context, information about the incremental risk and clinical presentation of CVD in T1DM needs greater clarity. Table 1 presents hazard ratios (HRs) of different CVDs in T1DM from selected important studies (8–10). Studies were chosen for inclusion by the writing group members; a formal evidence-based approach was not performed. Supplementary Table 1 presents detailed information from the current literature on the prevalence and incidence of CVD, CHD, and cerebrovascular disease in T1DM.

Overall, CVD events are more common and occur earlier in patients with T1DM than in nondiabetic populations;

Table 1—HRs for CVD, CHD, CVA, and PAD in patients with T1DM compared with healthy control subjects

Study name/PMID	Population	Study design	Diabetes duration, y	Study follow-up, y	HR
CVD					
UK GPRD: Soedamah-Muthu et al., 2006 (8) PMID: 16567818	7,479 with T1DM vs. 38,116 without DM; men and women, generally representative of the general UK population	Observational case-control cohort	15 ± 12	4.7	Myocardial infarction, coronary revascularization, stroke, acute CHD death: men, 3.6 (95% CI, 2.9–4.5); women, 7.6 (95% CI, 5.5–10.7)
CHD					
UK GPRD: Soedamah-Muthu et al., 2006 (8) PMID: 16567818	7,479 with T1DM vs. 38,116 without DM; men and women, generally representative of the general UK population	Observational case-control cohort	15 ± 12	4.7	Myocardial infarction, coronary revascularization, acute CHD death: men, 3.0 (95% CI, 2.2–4.1); women, 7.6 (95% CI, 4.9–12.0)
CVA					
Nurses' Health Study: Janghorbani et al., 2007 (9) PMID: 17389335	116,316 women aged 30–55 y in 1976–2002, 105,247 (90.5%) women without DM, 303 (0.3%) with T1DM, and 10,766 (9.2%) with T2DM; primarily white women but includes Hispanics, blacks, and Asians	Observational cohort	31.4 ± 14.3	24	Fatal or nonfatal stroke, excluding "silent" strokes: women, 5.9 (95% CI, 4.2–8.3) compared with women without DM
PAD					
Jonasson et al., 2008 (10) PMID: 18443192	31,354 patients with T1DM from the Swedish Inpatient Registry identified from 1975–2004 compared with the Swedish population; white northern Europeans	Administrative database, ICD-9 coding	ND	12.5	Incident nontraumatic lower-extremity amputations: 85.5 (95% CI, 72.9–100.3)

The hazard ratio (HR) is a measure of how often a particular event happens in one group compared with how often it happens in another group, over time. HRs are as reported in the publication (Soedamah-Muthu et al. [8], Janghorbani et al. [9]) or, when not available, are estimated from the data provided in the original publication (all others). CHD, coronary heart disease; CI, confidence interval; CVA, cerebrovascular disease; CVD, cardiovascular disease; DM, diabetes mellitus; EDC, Epidemiology of Diabetes Complications; GPRD, General Practice Research Database; ICD-9, *International Classification of Diseases, 9th Revision*; ND, not determined; PAD, peripheral artery disease; PMID, PubMed-indexed for MEDLINE; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; y, year.

women with T1DM are more likely to have a CVD event than are healthy women. CVD prevalence rates in T1DM vary substantially based on duration of DM, age of cohort, and sex, as well as possibly by race/ethnicity (8,11,12). The Pittsburgh Epidemiology of Diabetes Complications (EDC) study demonstrated that the incidence of major coronary artery disease (CAD) events in young adults (aged 28–38 years) with T1DM was 0.98% per year and surpassed 3% per year after age 55 years, which makes it the leading cause of death in that population (13). By contrast, incident first CVD in the nondiabetic population ranges from 0.1% in 35- to 44-year-olds to 7.4% in adults aged 85–94 years (14). An increased risk of CVD has been reported in other studies, with the age-adjusted relative risk (RR) for CVD in T1DM being ≈10 times that of the general population (15–17). One of the most robust analyses of CVD risk in this disease derives from the large UK General Practice Research Database (GPRD), comprising data from >7,400 patients with T1DM with a mean ± SD age of 33 ± 14.5 years and a mean DM duration of 15 ± 12 years (8). CVD events in the UK GPRD study occurred on average 10 to 15 years earlier than in matched nondiabetic control subjects.

Coronary Heart Disease

When types of CVD are reported separately, CHD predominates (Table 1; Supplementary Table 1). In the UK GPRD, T1DM was associated with a markedly increased adjusted HR for major CHD events compared with the general population during 4.7 years of follow-up in both men (adjusted HR, 3.6; 95% confidence interval [CI], 2.8–4.6) and women (adjusted HR, 9.6; 95% CI, 6.4–14.5) (8), similar to the RR of CHD associated with T2DM. The published cumulative incidence of CHD ranges between 2.1% (18) and 19% (19), with most studies reporting cumulative incidences of ≈15% over ≈15 years of follow-up (20–22). Cumulative CHD mortality rates over 14 to 18 years are reported as being between 6 and 8% (19,22), are higher in men than in women (23), and are higher in those >40 years of age than in those <40 years of age (23) (Supplementary Table 1). Of interest, myocarditis after myocardial infarction has been described recently in a mouse model, with some evidence that a similar complication occurs in T1DM patients (24–27).

Cerebrovascular Accident

Although stroke is less common than CHD in T1DM, it is another important CVD end point. Reported incidence rates vary but are relatively low. A study of blacks with T1DM found the cumulative incidence of cerebrovascular accidents was 3.3% over 6 years (≈0.6% per year) (12); the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) reported an incidence rate of 5.9% over 20 years (≈0.3%) (21); and the European Diabetes (EURODIAB) Study reported a 0.74% incidence of cerebrovascular disease per year (18). These incidence rates are for the most part higher than those reported in the general population, which are reported at ≈0.2–0.3% per year (14).

Peripheral Artery Disease

PAD is another important vascular complication of T1DM (Supplementary Table 2). There are several components of PAD, including occult disease, assessed by ankle-brachial index, extremity arterial calcification, and lower-extremity nontraumatic amputation. The data available on PAD focus on amputation. The rate of nontraumatic amputation in T1DM is high, occurring at 0.4–7.2% per year (28). By 65 years of age, the cumulative probability of lower-extremity amputation in a Swedish administrative database was 11% for women with T1DM and 20.7% for men (10). In this Swedish population, the rate of lower-extremity amputation among those with T1DM was nearly 86-fold that of the general population. Calcification of the extremity arteries was reported in 4.6% of the EDC cohort, more commonly in men, and in individuals >30 years of age (29). Predictors of all types of PAD include increasing age, male sex, history of foot lesions or ulcers, diastolic BP, low-density lipoprotein cholesterol (LDL-C), glycosylated hemoglobin (HbA_{1c}), DM duration, hypertension, albumin excretion rate, glomerular filtration rate (GFR), smoking status, and retinopathy (10,28,30,31). In a meta-analysis of 5 studies of T1DM patients, with each 1% increase in HbA_{1c} the risk of PAD increased by 18% (32). Interestingly, aggressive glycemic control to lower the HbA_{1c} did not appear to reduce rates of peripheral arterial occlusion in the DCCT/EDIC study but did reduce the incidence of peripheral arterial calcification (31).

Subclinical CVD

Abnormal vascular findings associated with atherosclerosis are also seen in patients with T1DM. Coronary artery calcification (CAC) burden, an accepted noninvasive assessment of atherosclerosis and a predictor of CVD events in the general population, is greater in people with T1DM than in nondiabetic healthy control subjects, as found in the Coronary Artery Calcification in Type 1 Diabetes (CACTI) Study (33). With regard to subclinical carotid disease, both carotid intima-media thickness (cIMT) and plaque are increased in children, adolescents, and adults with T1DM (online-only Data Supplement Table 3) compared with age- and sex-matched healthy control subjects (34–39). Traditional and glycemia-related risk factors such as age, DM duration, BMI, total cholesterol (TC) and LDL-C, BP, smoking, and albumin excretion rate are associated with cIMT and plaque in T1DM (35,36,38–41).

Endothelial function is altered even at a very early stage of T1DM (42,43), as discussed in the section on children. Interestingly, the extent of endothelial dysfunction correlated significantly with blood glucose levels and was inversely related to DM duration. Adults in the Pittsburgh EDC study who had markers of endothelial dysfunction were more likely to develop CHD (44). Taken together, these data suggest that preclinical CVD can be seen more frequently and to a greater extent in patients with T1DM, even at an early age. Some data suggest that its presence may portend CVD events; however, how these subclinical markers function as end points is not clear.

Cardiac Autonomic Neuropathy

Neuropathy in T1DM can lead to abnormalities in the response of the coronary vasculature to sympathetic stimulation, which may manifest clinically as resting tachycardia or bradycardia, exercise intolerance, orthostatic hypotension, loss of the nocturnal decline in BP, or silent myocardial ischemia on cardiac testing. These abnormalities can lead to delayed presentation of CVD. An early indicator of cardiac autonomic neuropathy is reduced heart rate variability, which can

be assessed qualitatively in the clinic as a relatively fixed heart rate of 80 to 90 bpm. Traditional CVD risk factors predict cardiac autonomic neuropathy, including BP, LDL-C, triglycerides, and central obesity (45). Limited data suggest silent myocardial ischemia is more common in the presence of cardiac autonomic neuropathy (46). Estimates of the prevalence of cardiac autonomic neuropathy in T1DM vary widely, in part because of differing definitions and methods of testing (heart rate variability, response to Valsalva maneuver, handgrip, multiple versus isolated abnormalities, etc.) (46). Cardiac neuropathy may affect as many as ≈40% of individuals with T1DM (45).

TIME COURSE OF CVD EVENTS

In all patients, those with DM included, the clinical presentation of CHD is very late in the pathophysiological process of atherosclerosis. This is suggested by the vascular abnormalities in cIMT and brachial artery studies (described in the section "Subclinical CVD") and by the delay in the onset of CVD experienced by patients in the intensive therapy intervention in the DCCT when no CVD was present at the onset of the study (47). That being said, CVD events occur much earlier in patients with T1DM than in the general population, often after 2 decades of T1DM, which in some patients may be by age 30 years. Thus, in the EDC study, CVD was the leading cause of death in T1DM patients after 20 years of disease duration, at rates of >3% per year (13). Rates of CVD this high fall into the National Cholesterol Education Program's high-risk category and merit intensive CVD prevention efforts (48). Nephropathy may also influence the timing of CVD events. Historical data suggest that CHD and PAD followed the development of overt nephropathy, which increased the CVD risk several fold (49). However, the decline in kidney disease in T1DM patients by >60% in the past several decades has not been accompanied by a corresponding fall in rates of CVD (50), which suggests that other factors contribute to CVD events.

CVD IN SPECIAL T1DM POPULATIONS

Sex

Rates of CVD are lower in premenopausal women than in men. In T1DM, these differences are erased. In the United Kingdom, CVD affects men and women with T1DM equally at <40 years of age (23), although after age 40 years, men are affected more than women (51). Similar findings on CVD mortality rates were reported in a large Norwegian T1DM cohort study (52) and in the Allegheny County (PA) T1DM Registry (13), which reported the relative impact of CVD compared with the general population was much higher for women than for men (standardized mortality ratio [SMR] 13.2 versus 5.0 for total mortality and 24.7 versus 8.8 for CVD mortality, women versus men). Rates of CAC in T1DM reflect the same trends. Both the U.S. CACTI (33) and Pittsburgh EDC (43) data and a separate British study (53,54) found that women with T1DM had at least as much CAC as men with T1DM. The reasons for excess CAC and its prominence in women are not clear, but the reported data suggest sex differences in CAC in patients with T1DM are explained by fat distribution patterns associated with insulin resistance (waist-to-hip ratio, waist circumference) (33,53,54). Another hypothesis is that lower levels of high-density lipoprotein cholesterol (HDL-C) explain the equalization of CAC between the sexes. Overall, T1DM appears to eliminate most of the female sex protection seen in the nondiabetic population.

Race/Ethnicity

Little is known about the relationship between race or ethnicity and CVD in T1DM. The available data are primarily in blacks. The New Jersey 725 is an exclusively black cohort of patients with T1DM identified and recruited through the New Jersey State Hospital database (12). Data from this cohort suggest CVD event rates are ≈8 times higher than what is reported in the white EDC study population. The Allegheny County childhood T1DM registry also included blacks and showed a twofold greater CVD mortality in black than in white county residents with T1DM (55). However, when SMRs were calculated against the background general population, CVD was increased in both races by ≈threefold, which suggests a general race-based disadvantage rather than a DM-specific effect (55). There is even less information about CVD risk factor burden in T1DM in other races/ethnicities. The DiaComp Study suggested similar rates of CVD risk factors across Asian, Hispanic, and non-Hispanic populations; however, the population was too young for CVD events (56). It should be acknowledged that any differences related to race or ethnicity could be genetic (T1DM acting differently based on race/ethnicity) or biological but mediated via other risk factors, such as hypertension, or related to socioeconomic factors. The exact contributions of these elements are not well delineated, and it may well be impossible to eliminate these types of potential confounding.

Pregnancy

Fewer than 0.5% of pregnancies are complicated by T1DM (57); however, risks to the mother and the child are greater than in those without T1DM. A full assessment for maternal CVD and DM complications should be made before or during pregnancy, or both, specifically for retinopathy, which may worsen during pregnancy, and for nephropathy and hypertension. Women with T1DM are at greater risk for preeclampsia, particularly if they have preexisting CVD (57,58). Pregnancy outcomes in mothers with T1DM are overall worse than in the general population, and women with known CVD and T1DM are at extremely high risk for poor fetal outcomes. Evidence-based recommendations for the prevention of preeclampsia have been published recently by the World Health Organization and include women with T1DM (59).

Children

CVD events are not generally expected to occur during childhood, even in the setting of T1DM; however, the atherosclerotic process begins during childhood. Children and adolescents with T1DM have subclinical CVD abnormalities even within the first decade of DM diagnosis according to a number of different methodologies, including flow-mediated arterial dilation (42,43,60,61), endothelial peripheral arterial tonometry (62), and arterial stiffness measured by pulse wave velocity (63). Studies on cIMT have been inconsistent, with some publications showing differences in cIMT between healthy children and those with T1DM (35,43,64,65), whereas others showed no difference (42,66,67). The largest published study measured cIMT in >300 children with T1DM who were

undergoing intensive insulin treatment and compared them with >100 healthy control subjects (34); cIMT was higher in boys but not in girls.

Longitudinal data about the effect of glycemic control during childhood on CVD events are quite limited. The best available information comes from the DCCT, which included 195 adolescents (68). Intensive control during adolescence resulted in delayed onset and progression of retinopathy and nephropathy but not CVD, likely because of the long latency to events (68). These benefits were thought by the authors to outweigh the almost threefold increased risk of hypoglycemia seen in this early trial. Subsequent experience and publications report lower rates of hypoglycemia when adolescents are treated intensively to achieve lower HbA_{1c} (69), which suggests concerns about high rates of hypoglycemia are likely unfounded.

CVD IN T1DM VERSUS T2DM

CVD in T1DM differs from T2DM, not only in that it presents at a younger age but also in that women are affected at rates equal to those in men. Risk factors appear to affect the risk for CVD differently in T1DM versus T2DM (Table 2). As described below, coronary findings may differ between T1DM and T2DM and from those in the general population, with some studies suggesting atherosclerosis in T1DM is more diffuse and more concentric.

Table 2—Relative association between specific cardiovascular risk factors and CVD events in T1DM versus T2DM

	T1DM	T2DM
Hypertension	+++	++
Cigarette smoke	++	++
Inflammation	++	++
High LDL-C	+	+++
Low HDL-C	0, +	++
Triglycerides	No data	++
Microalbuminuria	+++	+++
Insulin resistance	+	+++
Poor glycemic control	+++	+++

Range, 0 to +++. CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

PATHOLOGY OF THE ARTERIAL WALL IN T1DM

There is developing interest in the way in which the pathology of atherosclerosis in patients with DM differs from those without DM and the way in which atherosclerotic lesions in T1DM differ from those in T2DM. In a study of atherectomy samples that did not distinguish DM type, patients with DM appeared to have lesions that were more laden with lipids, macrophages, and thrombus than nondiabetic patients (70).

The data on atherosclerosis in T1DM are limited. A small angiographic study compared 32 individuals with T1DM to 31 nondiabetic patients matched for age and symptoms (71). That study found atherosclerosis in the setting of T1DM was characterized by more severe (tighter) stenoses, more extensive involvement (multiple vessels), and more distal coronary findings than in patients without DM. A quantitative coronary angiographic study in T1DM suggested more severe, distal disease and an overall increased burden compared with nondiabetic patients (up to fourfold higher) (72).

When T1DM is compared with T2DM, the characteristics of the atherosclerosis may differ, although the data are very limited. In the study by Burke et al. (73) discussed above, there was overall lower atherosclerotic burden in T1DM than in T2DM, although the number of T1DM patients was relatively small (n = 16). An earlier autopsy study suggested plaques in T1DM were soft and fibrous and had a more concentric (less eccentric) location of lesions (74). A small computed tomography study comparing patients with T1DM to those with T2DM demonstrated similar CAC scores but more obstructive lesions, more noncalcified lesions, and more lesions overall in patients with T2DM than in those with T1DM (75).

Techniques for demonstrating subclinical atherosclerosis, such as intravascular ultrasound or virtual histology, have been used to assess atherosclerotic lesions in patients with T1DM and are conflicting. Intravascular ultrasound shows that the degree of subclinical CAD is more severe in T1DM than in nondiabetic control subjects, which supports the autopsy data described above (76). However, another study using angiography and intravascular ultrasound suggested patients treated with insulin had less plaque burden than either patients with DM not treated with insulin or nondiabetic individuals, and the use of insulin was negatively associated with plaque area (less plaque area with insulin use) (77). In that study, DM type was defined by insulin use only, which makes it difficult to interpret these findings. In another small study, coronary artery plaque formation was significantly related to mean HbA_{1c} levels over time (78). In general, autopsy and angiographic studies have significant referral biases, and additional studies using more modern techniques are needed to better understand the nature of atheroma in patients with T1DM.

INFLAMMATION AND T1DM

In the general population, inflammation is a central pathological process of atherosclerosis (79). Limited pathology data suggest that inflammation is more prominent in patients with DM than in nondiabetic control subjects (70), and those with T1DM in particular are affected. Studies showed C-reactive protein is elevated within the first year of diagnosis of T1DM (80), and interleukin-6 and fibrinogen levels are high in individuals with an average disease duration of 2 years (81), independent of adiposity and glycemia (82). Other inflammatory markers such as soluble interleukin-2 receptor (83) and CD40 ligand (84,85) are higher in patients with T1DM than in nondiabetic subjects. Inflammation is evident in youth, even soon after the diagnosis of T1DM. Intensive treatment has been linked to decreases in soluble intercellular adhesion molecule type 1 and increases in soluble tumor necrosis factor-α receptor 1 in the DCCT (86).

Some data link inflammation in T1DM to CVD. Low adiponectin levels have been shown to predict both CAD events and CAC in patients with T1DM (87,88). In addition, levels of soluble interleukin-2 receptor correlated with CAC progression independent of traditional CHD risk factors in T1DM (83). Inflammatory markers also independently predicted CHD prevalence and outcomes in cohort studies of T1DM patients. White blood cell levels have been strongly associated with future CAD in T1DM (90). Other more novel inflammatory markers have also been connected with CVD, including lipoprotein-associated phospholipase A2,

C-reactive protein (91), serum endogenous secretory RAGE (receptor for advanced glycation end products) (92), plasma fibrinogen (93), modified apolipoprotein B–rich immune complexes (94), and connective tissue growth factor (95). Some factors have been reported primarily in the setting of diabetic nephropathy, such as plasma growth-differentiation factor 15 (96), asymmetric dimethylarginine (97), and osteoprotegerin (98).

The mechanisms by which inflammation operates in T1DM are likely multiple but may include hyperglycemia and hypoglycemia, excess adiposity or altered body fat distribution, thrombosis, and adipokines. Several recent studies have demonstrated a relationship between acute hypoglycemia and indexes of systemic inflammation (99), including increased CD40 expression and plasma soluble CD40 ligand concentration, greater platelet-monocyte aggregation (100), and increased circulation of plasminogen activator inhibitor, vascular endothelial growth factor, vascular adhesion molecules, interleukin-6, and markers of platelet aggregation (99). These studies suggest that acute hypoglycemia in T1DM produces complex vascular effects involved in the activation of proinflammatory, prothrombotic, and proatherogenic mechanisms. Excess adiposity, in general a proinflammatory state (101–103), is associated with both microvascular and macrovascular complications in T1DM (104,105). Levels of the adipokine leptin and its associated leptin receptor, which are involved in signaling satiety in the brain, are also increased in T1DM (106), and leptin may be proinflammatory (107). Additionally, the increased CD40 ligand expression and platelet-monocyte aggregation in T1DM may contribute to the accelerated rate of atherogenesis in these patients (108). Fibrinogen, a prothrombotic acute phase reactant, is increased in T1DM and is associated with premature CVD (109), and it may be important in vessel thrombosis at later stages of CVD.

GENETICS AND ATHEROSCLEROSIS IN T1DM

Genetic polymorphisms appear to influence the progression and prognosis of CVD in T1DM (Supplementary Table 4). The most well-developed illustration of this is the haptoglobin 2–2 genotype and its relationship to CAD in patients with T2DM and T1DM, as discussed below. Like fibrinogen, haptoglobin is an acute phase protein that inhibits hemoglobin-induced oxidative tissue damage by binding to free hemoglobin (110). Once bound, the haptoglobin-hemoglobin complex is cleared from the circulation either by the liver or through the scavenger receptor CD163, which is present on monocytes and macrophages (111). In humans, there are 2 classes of alleles at the haptoglobin locus, giving rise to 3 possible genotypes: haptoglobin 1-1, haptoglobin 2-1, and haptoglobin 2-2. The haptoglobin 1 protein allele has greater antioxidant function; it is more efficient in preventing heme release from haptoglobin-hemoglobin complexes and promoting uptake by the CD163 macrophage receptor (112–114). The haptoglobin 2 allele product has less antioxidant capacity because of its greater molecular mass (115), and in some studies, it is associated with impaired reverse cholesterol transport (114,116). The prevalences of haptoglobin genotypes in the EDC T1DM cohort were 11.5%, 41.3%, and 47.2%, respectively (117). In T1DM, there is an independent twofold increased incidence of CAD in haptoglobin 2-2 carriers compared with those with the haptoglobin 1-1 genotype (117); the 2-1 genotype is associated with an intermediate effect of increased CVD risk. More recently, an independent association was reported in T1DM between the haptoglobin 2-2 genotype and early progression to end-stage renal disease (ESRD) (118). In the CACTI study group, the presence of the haptoglobin 2-2 genotype also doubled the risk of CAC in patients free from CAC at baseline, after adjustment for traditional CVD risk factors (119). What is particularly exciting about these observations is the potential for preventing CVD with vitamin E in those with haptoglobin 2-2, as may occur in T2DM (120–123). The relevance of these observations to patients with T1DM remains unexamined, and the haptoglobin 2-2 genotype has not been identified by genome-wide association studies.

There are other genetic predispositions associated with CVD risk in T1DM. A number of polymorphisms have been evaluated against clinical and subclinical CVD end points in subjects with T1DM (see literature review in Supplementary Table 4). One haplotype has been identified that is associated with hematologic parameters and has also been associated with CAD and T1DM (124).

At present, genetic testing for polymorphisms in T1DM has no clear clinical utility in CVD prediction or management.

CVD RISK FACTORS AND MODIFIERS IN T1DM: PATHOPHYSIOLOGY, SCREENING, AND TREATMENT

Epidemiological studies have identified factors important to the incidence and prevalence of CVD in individuals with T1DM (Supplementary Table 1). These processes and biological factors could be important targets for risk reduction and include hypertension, proteinuria, obesity, HbA_{1c}, lipid levels, and smoking (Table 3). Of course, age and DM duration also play an important role. In addition, CVD risk brought on by unhealthy behaviors and associated CVD risk factors requires careful consideration. Avoidance of smoking, maintenance of a normal weight, and consumption of a balanced diet replete in fruits and vegetables, low in saturated fat and sodium, and enriched in whole grains are generally recommended. In this section, we will address a variety of risk factors and their relationship to CVD risk management.

Glycemic Control

Dysglycemia is often conceived of as a vasculopathic process. Preclinical atherosclerosis and epidemiological studies generally support this relationship. Clinical trial data from the DCCT supplied definitive findings strongly in favor of beneficial effects of better glycemic control on CVD outcomes.

Glycemia is associated with preclinical atherosclerosis in studies that include tests of endothelial function, arterial stiffness, cIMT, autonomic neuropathy, and left ventricular (LV) function in T1DM (16,39,126–132). The extent of atherosclerosis by intravascular ultrasound also correlated with HbA_{1c} over 18 years of follow-up in the Oslo Study; a 1% increase in mean HbA_{1c} was associated with a 6.4% increase in coronary vessel stenosis (78). Intensive DM therapy has been shown to prevent the increase in resting heart rate characteristic of patients with T1DM (133), and autonomic function was significantly

Table 3—Summary of CVD risk factor screening and treatment in T1DM

Risk factor	Screening test	Timing	Target	Actions to be considered	Professional organization recommendation
Hyperglycemia	HbA_{1c}, glucose monitoring	Every 3 mo	Adults: ≤7.0%; youth: age 13–19 y, <7.5%; age 6–12 y, <8.0%; age <6 y, <8.5%	Increased intensity of glucose monitoring and manipulation of insulin dosing	ADA
DKD	Urine albumin to creatinine ratio; estimated GFR	Yearly beginning 5 y after diagnosis		ACE inhibitor; keep BP <130/80 mmHg (adults) or <90th percentile (children)	ADA, NKF
Dyslipidemia	Fasting lipid profile	Adults: every 2 y if low-risk values	LDL <100 mg/dL; non–HDL-C <130 mg/dL	Optimize glycemic control; low saturated fat diet; optimize other CVD risk factors	NHLBI (ATP III and Integrated Pediatric Guidelines*), ADA, AAP, AHA
	Fasting lipid profile	Children aged 10–21 y, once every 3–5 y	LDL <100 mg/dL; non–HDL-C <130 mg/dL	Consider statins if LDL ≥100 mg/dL, recommended if LDL ≥160 mg/dL; once treated, LDL goal is <100–130 mg/dL	NHLBI (ATP III, Integrated Guidelines*), AAP, AHA
	Fasting lipid profile	Adults without CVD	LDL <100 mg/dL	Statins, goal LDL <100 mg/dL	NHLBI (ATP III), ADA
	Fasting lipid profile	Adults with CVD	LDL <70 mg/dL	Statins, goal LDL <70 mg/dL	NHLBI (ATP III), ADA
Hypertension	BP	Every visit	Adults: >140/80 mmHg, goal <130/80 mmHg; children: BP >95th percentile or >130/80 mmHg	Lifestyle modifications for those with BP >120/80 mmHg: low salt, high fruits and vegetables, regular exercise Medications for those with BP >140/80 mmHg, or 130/80 mmHg in some younger individuals: ACE or ARB inhibitor, add others as necessary to achieve normal BP	NHLBI (JNC 7), ADA
Prehypertension	BP	Every visit	Adults: 120–130/80–89 mmHg; children: BP 90th–95th percentile	Borderline BP: low salt, high fruits and vegetables; regular exercise	ADA
Thrombosis prevention	None	Age ≥21 y	Adults with CVD	Aspirin	NHLBI (ATP III)

AAP, American Academy of Pediatrics; ACE, angiotensin-converting enzyme; ADA, American Diabetes Association; AHA, American Heart Association; ARB, angiotensin receptor blocker; ATP III, Adult Treatment Panel III; BP, blood pressure; CVD, cardiovascular disease; DKD, diabetic kidney disease; GFR, glomerular filtration rate; HbA_{1c}, hemoglobin A_{1c}; HDL-C, high-density lipoprotein cholesterol; JNC, Joint National Committee; LDL, low-density lipoprotein; mo, month; NHLBI, National Heart, Lung, and Blood Institute; NKF, National Kidney Foundation; T1DM, type 1 diabetes mellitus; y, year.
*Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents (125).

better in patients with intensive DM management (134). LV mass and function improve with better glycemic control (126, 135,136).

Epidemiological evidence generally supports the relationship between hyperglycemia and clinical CHD events in T1DM. In a small study of 177 patients with T1DM, the incidence of CHD events over 7 years of follow-up appeared to be related to baseline HbA_{1c} (137). Three major prospective observational studies reported mixed results on this question. The EURODIAB Study did not show an association between HbA_{1c} and CHD after adjustment for other CVD risk factors; albuminuria was an important predictor (138). Ten-year follow-up data from the Pittsburgh EDC study failed to demonstrate an association between glycemia and CHD (139,140), although a later analysis did demonstrate a relationship to CAD mortality (13). In WESDR, HbA_{1c} was not associated with myocardial infarction ($P = 0.08$) but was associated with CVD mortality ($P < 0.001$) (21), a finding that was sustained after 20 years of follow-up (11).

A large Swedish database review recently reported a reasonably strong association between HbA_{1c} and CAD in T1DM (HR, 1.3 per 1% HbA_{1c} increase) (141).

The DCCT was a major prospective, randomized clinical trial that evaluated the effect of glycemic control on long-term DM complications (68). In this pivotal T1DM study, outcomes were compared between patients who were treated with intensive therapy (≥3 insulin injections daily or continuous subcutaneous insulin infusion) and frequent blood glucose monitoring versus conventional T1DM therapy (1 or 2 insulin injections per day). After mean follow-up of 6.5 years of 1,441 patients (aged 13–39 years) in the United States and Canada, the HbA_{1c} in the intensive therapy group was 7.2% compared with 9.0% in those treated with conventional therapy. Intensive DM therapy was associated with a significant reduction in the incidence and progression of microvascular complications. Not surprisingly, given the age of the patients and the relatively short duration of DM, few macrovascular events were seen (68). The patients in the DCCT were then followed up observationally, as reported in EDIC, which provided an opportunity to evaluate the impact of the initial intensive therapy on more advanced outcomes. During EDIC, the majority of DCCT study participants were treated with intensive therapy in their own clinical setting and followed up longitudinally for complications. Outcomes were analyzed on an intention-to-treat approach based on the participants' original DCCT assignment (142). The mean HbA_{1c} of the EDIC cohort was then ≈8% (47,143). Remarkably, after a follow-up of 17 years, the intensive therapy provided during the DCCT still translated into reduced CVD event rates, despite similar therapy and glycemic control after the DCCT ended. CVD events were lower in the original intervention group by 42% (95% CI, 9–63%; $P = 0.02$), and the combined end point of nonfatal myocardial infarction, stroke, or CVD death was 57% (95% CI, 12–79%; $P = 0.02$) less frequent than in the patients randomized to conventional treatment (47,143). This effect appeared to be explained mostly by the difference in HbA_{1c} during the DCCT, although after adjustment for microalbuminuria alone, the significance of the treatment group effect was reduced substantially from $P < 0.001$ to $P = 0.04$. The glycemic control effect was thus consistent with previous DCCT/EDIC reports on surrogate outcomes such as cIMT (144) and CAC (145). When all intensive therapy trials of T1DM were combined in a meta-analysis (≈1,800 patients), the combined RR for any macrovascular event in patients in the intensive control group was much lower than those treated with conventional therapy, at 0.38 (95% CI, 0.26–0.56) (146); however, the majority of these patients were from the DCCT, which likely influenced these results. Nevertheless, these findings support the recommendation that early optimal glycemic control in T1DM will have long-term benefits for CVD reduction.

There is evidence that improved glycemic control in adolescents is associated with decreased apolipoprotein B levels and less oxidative stress (147) and that poor glycemic control is associated with CVD risk factors. The SEARCH for Diabetes in Youth study showed that higher HbA_{1c} was independently associated with higher levels of total cholesterol, triglycerides, and LDL-C (148).

Obesity and Insulin Resistance

Obesity is a known independent risk factor for CVD in nondiabetic populations, but the impact of obesity in T1DM has not been fully established. Traditionally, T1DM was a condition of lean individuals, yet the prevalence of overweight and obesity in T1DM has increased significantly, as reported from the Pittsburgh EDC study (149,150) and the DCCT/EDIC. The prevalence of obesity (BMI ≥30 kg/m^2) increased from 1% of subjects at the DCCT baseline (secondary to eligibility criteria) to 31% at EDIC year 12 (151). This is related to epidemiological shifts in the population overall, tighter glucose control leading to less glucosuria, more frequent/greater caloric intake to fend off real and perceived hypoglycemia, and the specific effects of intensive DM therapy, which has been shown to increase the prevalence of obesity (152). Indeed, several clinical trials, including the DCCT, demonstrate that intensive insulin therapy can lead to excessive weight gain in a subset of patients with T1DM (152). Predicting which individuals with T1DM will go on to become obese would be useful to allow providers to direct intensive lifestyle management efforts appropriately.

The sum effect of increased adiposity on CVD risk in T1DM is not clear. On the one hand, increases in the prevalence of overweight and obesity may not always imply worse CVD outcomes. In the Pittsburgh EDC study, the optimal BMI for patients with T1DM, that is, the BMI associated with the lowest mortality, was between 25 and 30 kg/m^2, which is higher than that for the general population (150). The effect of obesity on mortality was largely accounted for by waist circumference, a measure of central obesity (150). The distribution of weight gain was further examined in the EDC study by use of dual-energy X-ray absorptiometry to explore whether greater gluteal-femoral adiposity was associated with reduced CVD risk factors, as has been reported in the general population. In a cross-sectional analysis, greater leg adiposity (as a percentage of total fat mass) was associated with less CHD in women with T1DM but not in men. However, there was a strong inverse correlation between percentage leg adiposity and percentage trunk mass (0.96), which makes it difficult to determine whether this is a specific protective feature of leg fat or merely reflects the relative lack of central fat (153).

As is true in the general population, central obesity in T1DM can be accompanied by increased CVD risk factors, including greater visceral adiposity, higher BP, adverse lipoprotein changes, and insulin resistance (151,152). Several studies have described metabolic syndrome in T1DM. Although T1DM is characteristically a disease of absolute insulin deficiency (154), insulin resistance appears to contribute to CHD risk in patients with T1DM. For example, having a family history of T2DM, which suggests a genetic predisposition for insulin resistance, has been associated with an increased CVD risk in patients with T1DM (155). Glucose disposal rate correlated with the extent of CAC in a Brazilian study of patients with T1DM (156). These observations have led to attempts to measure insulin resistance in T1DM. Measurement of insulin resistance is challenging in patients receiving insulin. Research studies have used regression equations derived from clamp studies; the derived estimated glucose disposal rate (157) predicts both CVD and diabetic nephropathy (158,159). Subsequent observations from the EURODIAB Study also suggested that insulin resistance–related risk factors predicted CHD events in patients with T1DM (138), and insulin resistance explains some portion of lipid abnormalities in young patients with T1DM (160).

Insulin resistance also appears to be an independent predictor of diabetic microangiopathy (158) and may be associated with impaired exercise capacity, LV hypertrophy, and diastolic dysfunction (161). More recently, a subgroup of the CACTI study underwent euglycemic clamps, and results showed that insulin resistance in T1DM patients compared with nondiabetic subjects was not related to their current level of glycemic control and yet predicted the extent of CAC (157).

Information on the modification of obesity or insulin resistance in patients with T1DM is limited. No systematic evaluation has been conducted to assess whether improving insulin sensitization lowers rates of CVD. Ironically, the better glycemic control associated with insulin therapy may lead to weight gain, with a superimposed insulin resistance, which may be approached by giving higher doses of insulin. However, some evidence from the EDC study suggests that weight gain in the presence of improved glycemic control is associated with an improved CVD risk profile (162). Some data are available on the use of metformin in T1DM as an insulin-sparing agent; however, greater understanding of the role of insulin sensitizers should be pursued as a possibly therapeutic advancement (163). How to measure insulin resistance, whether improving insulin sensitivity alters CVD outcomes, and the role and methods of lifestyle modification are areas that deserve further study.

It is prudent to recommend lifestyle changes to minimize excessive weight gain in T1DM, including caloric restriction when indicated and increased physical activity. These recommendations must be accompanied by appropriate patient education about frequent blood glucose monitoring accompanied by appropriate modifications in bolus or basal insulin administration with food intake and exercise to minimize the risk of hypoglycemia.

Dyslipidemia

In general, the lipid levels of adults with well-controlled T1DM are similar to those of individuals without DM, at least when participants in the DCCT were compared with the Lipid Research Clinic data (164). Worse glycemic control, higher weight (164), and more insulin resistance as measured by euglycemic clamp (165) are associated with a more atherogenic cholesterol distribution in men and women with T1DM (166). Better glycemic control can improve or normalize lipid values (167). The DCCT found sex-based variations in lipid values, with young women having higher LDL-C, higher levels of very low–density lipoproteins, and lower HDL-C and men having lower levels of very low–density lipoproteins and higher HDL-C than nondiabetic, similarly aged individuals. Studies in pediatric and young adult populations suggest higher lipid values than in youth without T1DM, with glycemic control being a significant contributor (148).

Most studies show that as is true for the general population, dyslipidemia is a risk factor for CVD in T1DM. Qualitative differences in lipid and lipoprotein fractions are being investigated to determine whether abnormal lipid function may contribute to this. The HDL-C fraction has been of particular interest because the metabolism of HDL-C in T1DM may be altered because of abnormal lipoprotein lipase and hepatic lipase activities related to exogenously administered insulin, and 1 study has shown that a particular subclass of HDL determined by nuclear magnetic resonance is associated with increased CHD risk in T1DM (168,169). Additionally, as noted earlier, the less efficient handling of heme by the haptoglobin 2-2 genotype in patients with T1DM leaves these complexes less capable of being removed by macrophages, which allows them to associate with HDL, which renders it less functional (116). Recent data from the EDC study suggest that the usual inverse association between HDL-C and CAD risk, although retained in men, is altered in women with T1DM, who show little increased protection with concentrations above the range of 50 to 60 mg/dL (170).

Conventionally, pharmacotherapy is used more aggressively for patients with T1DM and lipid disorders than for nondiabetic patients; however, recommendations for treatment are mostly extrapolated from interventional trials in adults with T2DM, in which rates of CVD events are equivalent to those in secondary prevention populations. Whether this is appropriate for T1DM is not clear, although epidemiological evidence from the EDC study does suggest that an LDL-C $>$100 mg/dL is associated with increased CVD risk (171), and a meta-analysis of LDL lowering that included T1DM patients suggested that LDL lowering reduces CVD events (although event rates were too small to be definitive) (172). Awareness of CVD risk and screening for hypercholesterolemia in T1DM have increased over time, yet recent data indicate that control is suboptimal, particularly in younger patients who have not yet developed long-term complications and might therefore benefit from prevention efforts (173).

Adults with T1DM who have abnormal lipids and additional risk factors for CVD (e.g., hypertension, obesity, or smoking) who have not developed CVD should be treated with statins. Adults with CVD and T1DM should also be treated with statins, regardless of whether they have additional risk factors.

Kidney Disease

Diabetic kidney disease (DKD) is a complication of T1DM that is strongly linked to CVD. DKD can present as microalbuminuria or macroalbuminuria, impaired GFR, or both. These represent separate but complementary manifestations of DKD and are often, but not necessarily, sequential in their presentation. Microalbuminuria, defined as an albumin excretion rate of 30 to 299 mg/24 h, is usually the earliest manifestation of DKD (174,175). Macroalbuminuria, defined as an albumin excretion rate $\geq$300 mg/24 h, is strongly associated with progressive loss of GFR and is traditionally used to define diabetic nephropathy (143,176). Impaired GFR, usually defined in T1DM as an estimated GFR (eGFR) $<60\ mL \cdot min^{-1} \cdot 1.73\ m^{-2}$, can occur at any time in DM but is less frequent than in the past (177,178). In both the EDC and the FinnDiane studies, the risk of all-cause mortality increased with the severity of DKD, from microalbuminuria to macroalbuminuria to ESRD. The presence of microalbuminuria or worse also fully accounted for all the excess mortality in these cohorts (159,179), in which, as indicated previously, CAD was the leading cause of death after 20 years' DM duration (13,68).

Microalbuminuria is likely an indicator of diffuse vascular injury. The fact that it can spontaneously remit suggests that it does not necessarily represent parenchymal kidney disease (178). Microalbuminuria is highly correlated with CVD (49,180–182). In the Steno Diabetes Center (Gentofte, Denmark)

cohort, T1DM patients with isolated microalbuminuria had a 4.2-fold increased risk of CVD (49,180). In the EDC study, microalbuminuria was associated with mortality risk, with an SMR of 6.4. In the FinnDiane study, mortality risk was also increased with microalbuminuria (SMR, 2.8). Some of the increased CVD and mortality risk associated with microalbuminuria may be mediated through the presence of other cardiovascular risk factors, such as hypertension, dyslipidemia, and insulin resistance. Improved glycemic control has reduced the incidence of microalbuminuria (175). A recent review summarized these data. In patients with T1DM and microalbuminuria, there was an RR of all-cause mortality of 1.8 (95% CI, 1.5–2.1) that was unaffected by adjustment for confounders (183). Similar RRs were found for mortality from CVD (1.9; 95% CI, 1.3–2.9), CHD (2.1; 95% CI, 1.2–3.5), and aggregate CVD mortality (2.0; 95% CI, 1.5–2.6). Adjusting for confounders left the data sets too small for adequate analysis. Similar results were observed for T2DM, with an RR of 1.9 (95% CI, 1.7–2.1) for all-cause mortality, 2.0 (95% CI, 1.7–2.3) for CVD mortality, and 2.3 (95% CI, 1.7–3.1) for CHD mortality; adjustment for confounders reduced these values only slightly.

Macroalbuminuria represents more substantial kidney damage and is also associated with CVD. Mechanisms may be more closely related to functional consequences of kidney disease, such as higher LDL-C and lower HDL-C. Prospective data from Finland indicate the RR for CVD is ≈10 times greater in patients with macroalbuminuria than in those without macroalbuminuria (184). Historically, in the Steno cohort, patients with T1DM and macroalbuminuria had a 37-fold increased risk of CVD mortality compared with the general population (49,180); however, a more recent report from EURODIAB suggests a much lower RR (8.7; 95% CI, 4.03–19.0) (185). For T2DM, the HR of macroalbuminuria for CVD death was somewhat smaller and varied from 1.89 (95% CI, 0.87–4.27) for an eGFR of >50 mL/min to 5.26 (95% CI, 2.73–10.2) for an eGFR of 30 to 59 mL/min; this effect was attributable in part to other CVD risk factors including HDL and hypertension (186). Taken together, these data suggest that the processes through which T1DM increases CVD risk are largely reflected by albuminuria (microalbuminuria and macroalbuminuria). It is encouraging that the DCCT/EDIC and Pittsburgh EDC studies suggest that the cumulative incidence of macroalbuminuria at 30 years' DM duration has decreased from a range of 17–25% to as little as ≈10% with the application of intensive DM therapy (187). However, these 2 studies also reveal that macroalbuminuria does not precede CAD events nearly as often as previously, consistent with the greater decline noted in ESRD than in CAD over time (187). Thus, the reduction in macroalbuminuria has not fully ameliorated the increased CVD risk, and a greater understanding of how to correct the processes that lead to microalbuminuria is clearly needed.

In general, impaired GFR is a risk factor for CVD, independent of albuminuria (188,189). In the CACTI study, lower GFR in T1DM was associated with increased risk of CAC progression (190). ESRD, the extreme form of impaired GFR, is associated with the greatest risk of CVD of all varieties of DKD. In the EDC study, ESRD was associated with an SMR for total mortality of 29.8, whereas in the FinnDiane study, it was 18.3. It is now clear that GFR loss and the development of eGFR <60 mL $\cdot$ min^{-1} $\cdot$ 1.73 m^{-2} can occur without previous manifestation of microalbuminuria or macroalbuminuria (177,178). In T1DM, the precise incidence, pathological basis, and prognosis of this phenotype remain incompletely described. In T2DM, low eGFR without albuminuria is becoming increasingly common over time and is associated with substantially increased risks of CVD and death (188,191,192).

A number of potential explanations have been proposed for the increased CVD risk associated with DKD in patients with T1DM. First, many risk factors for developing DKD and CVD overlap, including hyperglycemia, hypertension, dyslipidemia, obesity, and insulin resistance (193). Therefore, DKD may simply mark the severity and duration of these CVD risk factors. Second, DKD contributes to worsening of traditional CVD risk factors, for example, volume retention and renin-angiotensin-aldosterone system activation (which lead to increased BP), dyslipidemia (low HDL-C, high triglycerides, and a shift in LDL-C distribution to small, dense particles), and insulin resistance. DKD may also promote CVD through novel disease pathways, for example, an accumulation of asymmetric dimethylarginine, disruption of mineral metabolism, and anemia caused by erythropoietin deficiency, which contributes to LV hypertrophy (194). In addition, genome-wide association studies have identified several single-nucleotide polymorphisms associated with ESRD in some but not all studies (195–198).

Prevention of DKD remains challenging. Although microalbuminuria and macroalbuminuria are attractive therapeutic targets for CVD prevention, there are no specific interventions directed at the kidney that prevent DKD. Inhibition of the renin-angiotensin-aldosterone system is an attractive option but has not been demonstrated to prevent DKD before it is clinically apparent. However, some interventions targeting overall risk factors are likely to prevent DKD, including maintenance of euglycemia. In the DCCT, intensive DM therapy reduced the incidence of microalbuminuria and macroalbuminuria by 39% and 54%, respectively, and reduced impaired GFR by 50% (68,199). Effects of intensive DM therapy on impaired GFR were fully explained by treatment group differences in HbA_{1c} or albuminuria, which suggests that hyperglycemia drives both albuminuria and GFR loss in T1DM (199). The effects of intensive therapy on microalbuminuria, macroalbuminuria, and impaired GFR persisted beyond the duration of the DCCT ("metabolic memory") (143,199).

In contrast to prevention efforts, treatment of DKD with agents that inhibit the renin-angiotensin-aldosterone system is effective. The Collaborative Study Group's captopril trial demonstrated that angiotensin-converting enzyme (ACE) inhibitors reduce the progression of DKD and death in T1DM (200). Thus, once DKD develops, treatment is recommended to prevent progression and to reduce or minimize other CVD risk factors, which has a positive effect on CVD risk.

All patients with T1DM and hypertension or albuminuria should be treated with an ACE inhibitor. If an ACE inhibitor is not tolerated, an angiotensin II receptor blocker (ARB) is likely to have similar efficacy, although this has not been studied specifically in patients with T1DM. Optimal dosing for ACE inhibitors or ARBs in the setting of DKD is not well defined; titration may be guided by BP,

albuminuria, serum potassium, and creatinine. Combination therapy of ACE and ARB blockade cannot be specifically recommended at this time.

Hypertension

Hypertension is more common in patients with T1DM and is a powerful risk factor for CVD, regardless of whether an individual has DKD. In the CACTI study, hypertension was much more common in patients with T1DM than in age- and sex-matched control subjects (43% versus 15%, $P < 0.001$); in fact, only 42% of all T1DM patients met the Joint National Commission 7 goal (BP <130/80 mmHg) (201). Hypertension also affects youth with T1DM. The SEARCH trial of youth aged 3–17 years with T1DM ($n = 3,691$) found the prevalence of elevated BP was 5.9%, and minority ethnic groups, obese adolescents, and youth with poor glycemic control were affected disproportionately (202). Abnormalities in BP can stem from DKD or obesity. Hyperglycemia may also contribute to hypertension over the long term. In the DCCT/EDIC cohort, higher HbA_{1c} was strongly associated with increased risk of hypertension, and intensive DM therapy reduced the long-term risk of hypertension by 24% (203). Another small study of T1DM showed 29% of patients had hypertension; the hypertension correlated with disease duration and severity, particularly nephropathy (204), similar to findings from the EURODIAB Study (205). A recent analysis of the predictors of major T1DM outcomes in the Pittsburgh EDC study showed that although glycemic control diminished in importance over time, hypertension continued to be a strong CVD predictor (206). This may reflect the better glycemic control experienced by the later cohort, and perhaps the lack of amelioration of the profound adverse effects of hypertension on DM outcomes. This suggests that as glycemic control improves, standard risk factors gain importance.

There are few published trials about the ideal pharmacotherapeutic agent(s) for hypertension in T1DM. Observational data from the CACTI study showed 86% of patients were treated with ACE inhibitors and 14% were treated with ARBs (201). One small clinical trial (54 patients) of the effect of antihypertensive therapy on GFR compared nifedipine with enalapril in T1DM and demonstrated no difference in GFR or BP-lowering effect between the 2 drugs (207).

The American Diabetes Association (ADA) recommends a target BP of <140/80 mmHg for individuals with DM of both types. Given the increased risks of CVD and progressive kidney disease in T1DM, a lower BP goal of <130/80 mmHg may be appropriate in younger individuals. Lifestyle modification is recommended for all T1DM patients with BP >120/80 mmHg, with pharmacotherapy indicated at BPs above goal (208). Patients with T1DM and hypertension or albuminuria are usually treated with an ACE inhibitor.

In all children, experts recommend achieving or maintaining normal weight; an increase in consumption of fresh vegetables, fresh fruits, fiber, and nonfat dairy; and a reduction of sodium intake (209–211) in borderline BP, defined as systolic or diastolic BP between the 90th and 95th percentile for age, sex, and height percentile, whereas a BP >95th percentile should lead to consideration of the addition of pharmacotherapy (210), generally with an ACE inhibitor (212).

Tobacco and Smoking Cessation

Smoking is a major risk factor for CVD, particularly PAD (213); however, there is little information on the prevalence or effects of smoking in T1DM. The prevalence of smoking among patients with any type of DM was lower than in the general population in 1 study (214). The added CVD risk of smoking may be particularly important in patients with DM, who are already vulnerable. In patients with T1DM, cigarette smoking increased the risk of DM nephropathy, retinopathy, and neuropathy (214,215), possibly because of adverse effects on inflammation and endothelial function. Smoking increases CVD risk factors in T1DM via deterioration in glucose metabolism, lipids, and endothelial function (216). Unfortunately, smoking cessation can result in weight gain, which may deter smokers with DM from quitting (217). There is no evidence regarding the efficacy and safety of smoking cessation pharmacotherapy in patients with T1DM. This is an important area for future research.

Smoking cessation should be strongly recommended to all patients with T1DM as part of an overall strategy to lower CVD, in particular PAD.

CVD Risk Factors in Children With T1DM

CVD risk factors are more common in children with T1DM than in the general pediatric population (218). Population-based studies estimate that 14–45% of children with T1DM have ≥2 CVD risk factors (219–221). As with nondiabetic children, the prevalence of CVD risk factors increases with age (221). Interestingly, girls appear to have a higher risk factor burden than boys. A study of Norwegian children with T1DM showed girls were more likely to have elevated LDL-C and decreased HDL-C than boys (220). Similarly, a very large German study of >33,000 children and adolescents with T1DM found girls had a higher prevalence of high HbA_{1c} (≥7.5%), BMI >97th percentile, TC >200 mg/dL, LDL-C >130 mg/dL, and BP ≥90th percentile, whereas boys were more likely to have low HDL-C (<35 mg/dL) (222). In a U.S. cross-sectional study of 535 children with T1DM, Urbina et al. (63) demonstrated higher LDL-C, BP, glucose, and BMI than in healthy control subjects. In a longitudinal study of 360 subjects with T1DM, repeated lipid measurements identified sustained lipid abnormalities, for example, TC ≥200 mg/dL (16.9%), HDL-C <35 mg/dL (3.3%), and non–HDL-C ≥130 mg/dL (27.8%), ≥160 mg/dL (10.6%), and ≥190 mg/dL (3.3%) (223). HbA_{1c} was significantly related to TC and non–HDL-C, and BMI *z* score was inversely related to HDL-C. It is not clear whether these abnormalities can be explained by excess adiposity.

Children with T1DM are not immune to the pediatric obesity epidemic and its associated metabolic risk factors (224). Excess adiposity affected 38.5% of 283 children with T1DM, a rate higher than that of the U.S. pediatric population, and youth with T1DM have been reported to have features of the metabolic syndrome, including abdominal obesity, dyslipidemia, and hypertension (150,225,226). Compared with the children with T1DM who were of normal weight, overweight or obese children with T1DM had a higher prevalence of metabolic syndrome, hypertension, and fatty liver (226). Some studies have attempted to tease out whether weight or glycemic control is a more important determinant of CVD risk factors. A small Dutch study compared overweight children with T1DM to overweight children without T1DM; those

without DM had higher LDL-C and lower HDL-C (227).

Although pediatric lipid guidelines include some guidance relevant to children with T1DM (125,228,229), there are few studies on modifying lipid levels in children with T1DM. A 6-month trial of dietary counseling in Italian children and adolescents produced a significant improvement in TC/HDL-C, LDL-C, and non–HDL-C (218). Another lifestyle intervention trial of 196 adolescents with T1DM demonstrated improvement in lipid levels along with decreases in waist circumference, BMI, and insulin requirement with 6 months of exercise (230). In that trial, no correlation was seen between duration of DM and lipid levels; however, elevated triglycerides, TC, and LDL-C were seen in 50%, 45%, and 15% of patients, respectively. Few studies have specifically examined the effect of intensive pharmacological therapy on CVD risk factor reduction in children with T1DM, although 1 study suggested a trend toward improved endothelial function after 12 weeks of atorvastatin 20 mg/d (231).

The American Academy of Pediatrics, the American Heart Association, and the ADA recognize patients with DM, and particularly T1DM, as being in a higher-risk group who should receive more aggressive risk factor screening and treatment than nondiabetic children (125,228,229,232). The National Heart, Lung, and Blood Institute Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents has specific lifestyle and pharmacotherapy recommendations for children with lipid abnormalities and specifies management for children with T1DM (125). The recommendations in these pediatric guidelines are based on adult studies or on studies of preclinical atherosclerosis, because there are no trials in children with or without T1DM that show a relationship between treatment cut points in childhood and future CVD events. The available data suggest many children and adolescents with T1DM do not receive the recommended treatment for their dyslipidemia and hypertension (220,222). The ongoing multicenter Adolescent Type 1 Diabetes Cardio-Renal Intervention Trial (AdDIT) is a large intervention study examining the effect of ACE inhibitors and statins in adolescents with T1DM and high albumin excretion (233). This may provide more information about the use of statins and ACE inhibitors in high-risk pediatric patients with T1DM.

The National Heart, Lung, and Blood Institute Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents recommends lifestyle modification (125), and if lifestyle therapy is insufficient, pharmacotherapy is recommended for children aged ≥10 years with an LDL-C level ≥130 mg/dL (228,229).

ASSESSMENT OF CVD BURDEN

There are no CVD risk-prediction algorithms for patients with T1DM in widespread use. In the absence of data to the contrary, one approach to identifying CVD in patients with T1DM is to apply the same CHD risk-assessment and diagnostic strategies used in the general population. These recommendations are summarized in the American College of Cardiology Foundation/American Heart Association "Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults" (234). Use of the Framingham Heart Study and UK Prospective Diabetes Study (UKPDS) algorithms in the EDC study population did not provide good predictive results, which suggests that neither general or T2DM risk algorithms are sufficient for risk prediction in T1DM (235). On the basis of these findings, a model has been developed with the use of EDC cohort data (236) that incorporates measures outside the Framingham construct (white blood cell count, albuminuria, DM duration). Although this algorithm was validated in the EURODIAB Study cohort (237), it has not been widely adopted, and diagnostic and therapeutic decisions are often based on global CVD risk-estimation methods (i.e., Framingham risk score or T2DM-specific UKPDS risk engine [http://www.dtu.ox.ac.uk/riskengine/index.php]). Other options for CVD risk prediction in patients with T1DM include the ADA risk-assessment tool (http://main.diabetes.org/dorg/mha/main_en_US.html?loc=dorg-mha) and the Atherosclerosis Risk in Communities (ARIC) risk predictor (http://www.aricnews.net/riskcalc/html/RC1.html), but again, accuracy for T1DM is not clear. Both the American College of Cardiology Foundation/American Heart Association guideline and the ADA Standards of Medical Care in Diabetes discourage routine CHD screening beyond resting ECGs in patients with DM who do not have CVD symptoms or an abnormal ECG, favoring instead global risk factor assessment and treatment (234,238). However, neither of these guidelines differentiates between T1DM and T2DM, even though risk predictors may differ substantially between the 2 groups, and clinical judgment is required. In particular, individuals with DKD should be evaluated carefully for CVD.

Conventional CVD Testing

Patients with T1DM should not, a priori, have routine stress testing. As is true for the general population, the recommendation of ADA/American College of Cardiology/American Heart Association guidelines for any patient (including those with T1DM) who has symptoms suggestive of CHD, an abnormal resting ECG, or clustering of CVD risk factors that yields an intermediate or high global risk estimate (by Framingham or Reynolds risk score) is for that patient to have additional testing for CHD (234,238). For patients able to walk on a treadmill without significant baseline ST-segment abnormality, exercise treadmill testing remains the first-line diagnostic test based on its high cost-effectiveness and widespread availability. However, exercise treadmill testing may not be possible because of peripheral neuropathy, foot pathology, lower-extremity amputation, or ECG abnormalities of LV hypertrophy in patients with T1DM. Pharmacological stress imaging studies such as vasodilator myocardial perfusion imaging or pharmacological stress echocardiography may be required. The cost of these tests is three- to fivefold higher than a standard exercise treadmill test, and the diagnostic accuracy of this noninvasive testing modality may differ in T1DM compared with the general population.

Advanced and Novel CVD Testing

Advanced testing may be useful in patients with T1DM. CAC, assessed by computed tomographic imaging and used as a research tool in patients with T1DM (54,145), is seen at higher rates in patients with T1DM than in those without DM (53), and progression as defined by increases in CAC score is reduced by intensive glycemic control (145). In the Pittsburgh EDC study, 302 adults with T1DM underwent CAC screening at a mean age of 38 years. The prevalence of

CAC was 11% in patients <30 years of age and as high as 88% among those 50- to 55-years-old (54). CAC was independently associated with prevalent CHD across the entire cohort, with a stronger graded association in men than in women. In CACTI, CAC was present in 39% of males with T1DM and 12% of female participants. Interestingly, both men and women who had CAC were older and were more commonly affected with excess weight, including higher BMI, more intra-abdominal and subcutaneous fat, a larger waist circumference, and a higher waist-to-hip ratio (239). Although CAC assessment has been proven to predict subsequent CVD risk in the general population (240) and in cohorts of patients with T2DM (241), no data are yet available that analyze the utility of CAC assessment for risk prediction in T1DM.

It is reasonable to apply the current guidelines for the use of CAC assessment in T1DM, as recommended for the general population (234,240).

Other CVD testing modalities are less useful in assessing CVD in the individual patient. As noted above, T1DM prevalence and duration are associated with increased cIMT (37,39,144); however, the association between increased cIMT and subsequent CHD risk in this patient population is unknown, and its routine clinical use has not been recommended. Other advanced modalities for CVD screening and risk assessment have been correlated with cardiovascular risk markers and disease, such as the assessment of endothelial dysfunction by flow-mediated dilation/brachial artery reactivity (242) and cardiac magnetic resonance imaging methods (182), but these have failed to gain favor for broad clinical use and remain largely research-based assessments.

OPPORTUNITIES FOR ADVANCES

We have reviewed available data on CVD in T1DM, noting areas where understanding is lacking. We acknowledge that many of these data may be historical and that better glycemic control is changing the landscape of atherosclerosis in T1DM. More aggressive management of CVD risk factors and of the disease itself is likely to have a positive effect on CVD event rates. Although the increased rate of CVD in T1DM is well documented, understanding the cellular and molecular pathophysiology is an area of active research that promises to inform the clinical care of both patients with T1DM and those with T2DM. Care should be taken to distinguish contributors to macrovascular disease from those that promote microvascular disease. More insight is needed into the development of the atherosclerotic lesion itself and its natural history. Knowledge of the clinical role of inflammatory markers in T1DM and CVD prediction and management is in its infancy, but early data suggest a relationship with preclinical atherosclerosis. Novel processes, including inflammation and genetically based pathways, are beginning to be evaluated, along with tests for preclinical disease, with the hope of accelerating this understanding. However, the influence of these processes and other novel biomarkers on the accuracy of risk prediction over and above traditional risk-estimating models is unclear, especially in the population of patients with T1DM. Much work remains to be done to improve our understanding of T1DM and to help ameliorate the CVD effects of this important disease.

The following specific questions and comments about CVD in T1DM deserve attention:

Pathophysiology

- What is the basis for the increased CVD risk in T1DM?
- Is autonomic neuropathy an important explanatory process?
- What are the similarities and differences in atherosclerotic plaque in patients with T1DM compared with those without DM and in relation to insulin therapy?
- What are the relative contributions of DKD, obesity, insulin resistance, inflammation, hypertension, and dyslipidemia to CVD in T1DM?
- Does the hyperglycemia of T1DM promote calcification?
- What genetic factors are associated with CVD in T1DM? Large studies with well-powered validation cohorts are needed.
- What differs in the natural history of acute myocardial infarction in T1DM compared with T2DM and nondiabetic populations?
- Is myocarditis common immediately after an acute myocardial infarction in T1DM, and is there a DM-specific pathophysiology?
- How common is cardiomyopathy caused by coronary microangiopathy in T1DM, and what is its pathophysiology?
- What are the similarities and differences between heart failure in patients with and without T1DM?
- How does PAD differ between DM types and in people with DM compared with those without DM? What is the role of neuropathy?

Epidemiology and Risk Prediction

- Can CVD risk-estimation methods specific to T1DM be further developed?
- What is the role, if any, of cIMT and CAC in CVD risk prediction?
- Are there racial and ethnic differences in CVD risk factors and CVD events, and do these have implications for treatment?
- Is there a better way to assess insulin resistance in T1DM?
- Can novel biomarkers identify patients at the highest risk for clinical CVD outcomes?

Treatment

- What is the role of CVD risk factors in children with T1DM, and what are the indications for intervention?
- What are the efficacy and safety of lipid-lowering and antihypertensive therapy in adults and children?
- When should statins be initiated in T1DM?
- Can pharmacological approaches be safely used to promote smoking cessation in T1DM?
- Can ARBs safely and effectively prevent nephropathy-related CVD in T1DM?
- What are the best lifestyle modification interventions in T1DM that optimally adjust insulin administration to minimize the risk of hypoglycemia and reduce the risk for CVD?

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