

Report of the National Heart, Lung, and Blood Institute–National Institute of Diabetes and Digestive and Kidney Diseases Working Group on Cardiovascular Complications of Type 1 Diabetes Mellitus

Peter Libby, MD; David M. Nathan, MD; Kristin Abraham, PhD; John D. Brunzell, MD; Judith E. Fradkin, MD; Steven M. Haffner, MD, MPH; Willa Hsueh, MD; Marian Rewers, MD; B. Tibor Roberts, PhD; Peter J. Savage, MD; Sonia Skarlatos, PhD; Momtaz Wassef, PhD; Cristina Rabadan-Diehl, PhD

Cardiovascular disease (CVD) constitutes the major cause of mortality and morbidity in both type 1 (T1D) and type 2 (T2D) diabetes patients. Although the microvascular complications of T1D are well studied, macrovascular CVD, its treatment, and link to diabetes have been investigated primarily in T2D patients. On April 27 and 28, 2003, the National Heart, Lung, and Blood Institute (NHLBI) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) sponsored a meeting to identify ways to close gaps in our knowledge about CVD in T1D to improve prevention and treatment. Participants were asked to: (1) Evaluate opportunities for studying the pathogenesis of CVD in T1D patients. Risk factors unique to these patients were of particular interest, as well as studies of the cause of CVD in T1D with respect to existing databases or cohorts and involving partnerships between basic and clinical investigators. (2) Evaluate opportunities for intervention studies to treat or prevent CVD in T1D. Because of practical obstacles (recruitment, duration, and cost of interventional studies with hard clinical end points), identification of reliable methods and markers that enable efficient intervention were a high priority.

The meeting included 3 sessions: (1) current understanding of T1D and CVD; (2) opportunities to expand our understanding of the pathogenesis and clinical course of CVD in T1D; and (3) opportunities for intervention studies to reduce cardiovascular complications in T1D. This report summarizes the presentations made and concludes with recommendations drawn from the presentations and discussion among the participants.

Current Understanding of T1D and CVD

The epidemic of T2D in the United States has focused renewed attention on its complications. The complication causing greatest

mortality and expense is CVD, responsible for 65% to 75% of deaths in the T2D population. T1D is comparatively uncommon and usually has its onset in younger populations. Although not associated with many of the CVD risk factors recognized in T2D, the age-adjusted relative risk for CVD in T1D may even exceed that in T2D.¹ Relatively little is known about risks for CVD specific to T1D, except the substantial risk imparted by renal disease.¹ The mechanism(s) by which glycemia affects CVD through microvascular complications, secondary metabolic changes, or some direct effect requires further exploration. Such effects may be best appreciated in T1D, isolated from risk factors commonly accompanying T2D.

Studies in T2D have demonstrated benefits of blood pressure control, lipid lowering, and aspirin on CVD. No study has conclusively addressed the effects of glycemic control on CVD events in T1D patients. However, the Epidemiology of Diabetes Interventions and Complications (EDIC) study, a long-term follow-up of the Diabetes Control and Complications Trial (DCCT), used ultrasonographic measurements of carotid intimal-medial thickness (IMT), a marker for atherosclerosis that correlates with clinical events. The group that received intensive therapy during the DCCT had slower progression of IMT than the conventional-therapy group, as measured ≈ 6 years after the DCCT ended.²

Several factors might contribute to the endothelial dysfunction and accelerated atherosclerosis observed in patients with diabetes, even in the absence of kidney disease. Hyperglycemia, increased circulating fatty acid levels, altered lipoproteins, and derivatives of glycation and oxidation can damage the vascular endothelium, leading to endothelial dysfunction with proinflammatory and prothrombotic changes. Endothelial cell oxidative stress, activation of protein kinase C and other signaling pathways, and increased expression of adhe-

From Brigham and Women's Hospital (P.L.), Boston, Mass; MGH Diabetes Center (D.M.N.), Boston, Mass; National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health (K.A., J.E.F., B.T.R.), Bethesda, Md; University of Washington (J.D.B.), Seattle; University of Texas Health Science Center at San Antonio (S.M.F.); University of California (W.H.), Los Angeles; University of Colorado (M.R.), Denver; and National Heart, Lung, and Blood Institute, National Institutes of Health (P.J.S., S.S., M.W., C.R.-D.), Bethesda, Md.

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Correspondence to Cristina Rabadan-Diehl, PhD, Division of Heart and Vascular Diseases, NHLBI, NIH, Rockledge II, Room 10186, 6701 Rockledge Dr, Bethesda, MD 20892-7956. E-mail rabadanc@nhlbi.nih.gov

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sion molecules are potential mechanisms that might lead to these changes and are currently under investigation.³

T1D subjects show impairment in endothelium-dependent vasodilatation,⁴ an effect dependent on the level of the endogenous vasodilator nitric oxide (NO). Furthermore, smooth muscle function appears impaired in T1D, and arterial vasodilatation in response to endothelium-independent agonists is blunted.⁴ Atherosclerosis is fundamentally an inflammatory condition⁵. In general, elevated triglycerides and reduced HDL, combined with accumulation of small, dense LDL particles, can prove proinflammatory by several mechanisms. Some fractions of HDL possess anti-inflammatory properties.⁶ The dyslipidemia of uncontrolled diabetes may also prove proinflammatory, thereby contributing to the early onset and fast progression of atherosclerosis in these patients. Diabetic individuals also exhibit a thrombotic diathesis deriving from increased platelet activation, overexpression of plasminogen activator inhibitor-1 (PAI-1), and increased levels of fibrinogen, both acute-phase reactants elevated in inflammatory states.⁷

Hyperglycemia can augment the production of proteins modified by advanced glycation end products (AGEs).⁸ AGE-modified macromolecules can bind the receptor for AGE (RAGE) in vascular cells and leukocytes. RAGEs promote inflammation and oxidation, particularly in cells involved in atherogenesis. Indeed, interruption of RAGE signaling can attenuate atherogenesis.⁹

Opportunities for Research on the Pathogenesis and Clinical Course of CVD in T1D

Metabolic Syndrome and CVD

The incidence of CVD in DCCT subjects was quite low,¹⁰ but the mean age of participants at the end of the study was only 33 years (range, 18 to 45). Recent clinical practice changes might have helped keep the rate low, and indeed, the incidence of cardiovascular events was also low in the control group. Nevertheless, the slower progression of subclinical atherosclerosis as measured by IMT in EDIC subjects compared with the standard-therapy group remained striking, well after the intervention phase of the study had ceased,² underscoring the potential long-term benefits of tight glucose control.

However, intensive diabetes therapy in the DCCT frequently caused excessive weight gain (25% of subjects), and those who gained excessive weight were much more likely to develop components of the metabolic syndrome, including dyslipidemia and hypertension.¹¹ As expected, microalbuminuria preceded hypertension in the control group, but the reverse was true in the intensive-therapy arm.¹² Therefore, in the past decade, the metabolic syndrome may have displaced nephropathy as the important precursor for CVD in patients with T1D. The ongoing availability of samples and data from the EDIC study provides a strong rationale and an excellent opportunity to study the development of the metabolic syndrome and its effect on the risks for CVD and nephropathy in T1D patients.

Endothelial Dysfunction in T1D and Insulin Resistance

Endothelial dysfunction is a well-accepted marker of vascular injury and predicts coronary artery events. The etiology of

TABLE 1. Adipocyte-Derived Cytokines

Adipokine	Action
TNF- α	Inhibits insulin signaling \rightarrow insulin resistance Activates inflammatory pathways, including NF- κ B
Leptin	\downarrow Insulin sensitivity in obesity promotes inflammation $\uparrow \uparrow$ Blood pressure
PAI-1	Impaired fibrinolysis $\uparrow \uparrow$ Tissue fibrosis, activates cells by binding to urokinase plasminogen activator receptor
IL-6	Stimulates liver production of C-reactive protein Promotes inflammation
Angiotensinogen	Precursor to angiotensin II, a vasoconstrictor, proinflammatory and pro-oxidant mediator
Adiponectin	$\uparrow \uparrow$ Insulin-mediated glucose uptake \downarrow Hepatic glucose production \downarrow Inflammation, prevents atherosclerosis in rodent models

TNF indicates tumor necrosis factor; NF, nuclear factor; and IL, interleukin.

vascular dysfunction is unknown. Insulin stimulates endothelial NO synthase, but this action is blunted by insulin resistance.¹³ Chronic infusion of insulin into normal subjects has resulted in endothelial dysfunction,¹⁴ so whether insulin is a vascular culprit in the setting of insulin resistance remains to be determined. The adipocyte is an increasingly recognized source of circulating cytokines (adipokines) that affect both insulin-mediated glucose uptake and vascular inflammation.¹⁵ Although adipokines like tumor necrosis factor- α , leptin, PAI-1, interleukin-6, and angiotensinogen are proinflammatory, adiponectin is atheroprotective through anti-inflammatory and antiatherogenic effects (Table 1). Low plasma adiponectin levels have been associated with the progression of coronary artery calcification (CAC) in T1D and nondiabetic subjects, independent of other cardiovascular risk factors.¹⁶ Thus, excess adiposity and the consequent state of inflammation may contribute to endothelial dysfunction in people with T1D.

Hyperglycemia itself contributes to endothelial dysfunction in both T1D and T2D, but the mechanisms remain unknown. Infusion of glucose into healthy subjects impairs brachial artery endothelium-dependent vasodilatation when stimulated with methacholine chloride, suggesting that hyperglycemia alters endothelial NO bioavailability.¹⁷ Inhibition of endothelium-derived NO might provide a possible mechanism by which hyperglycemia affects endothelial function in diabetic patients. Multiple mechanisms may explain the deleterious effects of hyperglycemia on the vessel wall. These include alteration of cell signaling pathways, including activation of protein kinase C β ; formation of AGE products that bind to receptors on tissues; enhancement of oxidation; increased thrombosis; and inflammation.⁸ Indeed, several studies have demonstrated endothelial dysfunction in T1D.^{4,18,19} Streptozotocin-induced diabetes can increase atherosclerosis in genetically prone apolipoprotein E-deficient mice, although this finding might result from the increased serum cholesterol associated with the mutation.⁹ Thus, other approaches that create T1D in mice also require examination to unravel the mechanisms of hyperglycemia in atherosclerosis development.

A better understanding of mechanisms that underlie the relation between central obesity and the earliest stages of

albuminuria may lead to improved therapies for both CVD and renal disease. If weight gain with intensive diabetic therapy proves to be related to worse cardiovascular outcomes, modification of clinical care may need to be considered. Prevention of weight gain and therapy aimed at specific components of the metabolic syndrome require further investigation.

Opportunities for Intervention Studies to Reduce Cardiovascular Complications in T1D Patients

Incidence of Coronary Artery Disease and Risk Factors

The incidence of coronary artery disease (CAD) is $\approx 1\%$ to 2% per year among young, asymptomatic persons with T1D.^{20,21} By their mid-40s, $>70\%$ of men and 50% of women with T1D develop CAC,²² a marker of atherosclerotic plaque. CAD is the main cause of death in persons with T1D. By age 55, 35% of T1D patients die of CAD in contrast to only 8% of nondiabetic men and 4% of women.¹ Accelerated atherosclerosis and diabetic cardiomyopathy contribute to the excess mortality. Compared with the general population, in T1D patients atherosclerosis occurs earlier in life, is more diffuse,²³ and leads to higher case fatality,^{24,25} higher cardiac failure²⁶ and restenosis rates,²⁷ and shorter survival.²⁸ Women with T1D are affected as often as men and are 9 to 29 times more likely to die of CAD than nondiabetic women; the risk for men is increased 4- to 9-fold.^{1,29} In a broader context, as much as 10% of premature CAD morbidity and mortality in the general population is due to T1D.

T1D patients with proteinuria have a 15 to 37 times increased risk of fatal CAD, whereas the risk for those without proteinuria is 3- to 4-fold compared with the general population.^{1,30} The cumulative incidence of clinical CAD within 6 years after onset of proteinuria is 40% , versus 5% in patients without proteinuria.³¹ The traditional view is that T1D patients rarely develop severe CVD unless they have proteinuria or renal failure and that the excess risk is due to CAD rather than cardiomyopathy.³² However, the temporal and causal relation between CAD and diabetic nephropathy remains unresolved. An increasing body of evidence suggests that these 2 complications of T1D share risk factors and develop in parallel^{33,34} rather than CAD being a consequence of dyslipidemia and hypertension of nephropathy. Interestingly, LDL and HDL cholesterol levels may be more favorable in T1D patients than in nondiabetic controls.³⁵ However, patients with T1D have qualitative abnormalities, such as a preponderance of small, dense LDL particles of particular atherogenicity. Chronic inflammation, marked by elevated white blood cell counts²⁰ or C-reactive protein levels,³⁶ is also associated with clinical CAD and CAC in T1D.

Chronic hyperglycemia has had an uncertain link to the development of macrovascular complications of T1D until recently. Studies ascertaining traditional clinical CAD end points in relatively poorly controlled patients gave mixed results.^{20,21} In contrast, a study with electron beam tomography repeated during a 3-year follow-up demonstrated a 7-fold greater progression of CAC in patients with a glycosylated hemoglobin (HbA1c) value $>7.5\%$ compared with those with a lower HbA1c.³⁷ Similarly, DCCT participants on conventional treatment (mean HbA1c, 9%) had a greater 6-year

TABLE 2. Potential Intervention Goals to Prevent CAD in T1D

Control of hyperglycemia
Control of hypertension
Blood pressure $<120/80$
Control of dyslipidemia
LDL <70 mg/dL, HDL >45 mg/dL, triglycerides <150 mg/dL
Control of insulin resistance
Optimal insulin therapy (pump, closed loop)
Physical activity, weight maintenance
Insulin sensitizers?
Other
Aspirin/thienopyridines
Antiinflammatory agents

progression of carotid IMT than did the intensively insulin-treated participants (mean HbA1c, 7.2%).²

In summary, patients appear to have similar determinants of CAD in T1D and T2D, although the relative importance of hyperglycemia, dyslipidemia, and insulin resistance may differ. Additional information could emerge from existing observational studies seeking more understanding of rates of clinical events, rates of progression in surrogate end points, and their relevance to clinically significant disease. Risk factor patterns, including genetic interactions, need further study. Population-based data sources should yield estimates of awareness, treatment, and control of major CAD risk factors in the general population of T1D patients.

Potential Interventions to Prevent CAD in T1D Patients

Existing clinical data do not adequately address the potential impact of recent improvements in T1D management on CAD outcomes. At least 4 types of intervention may be effective for primary prevention of CAD in T1D patients, although controlled clinical trials have not yet established any of these modalities (Table 2). The advent of insulin analogs and pumps has made it possible to safely lower HbA1c below 7% in many adults with T1D. Reduction of insulin resistance can be accomplished through optimized insulin therapy, increased physical activity, weight control, and insulin-sensitizing drugs (although they are rarely used in T1D). Practitioners increasingly prescribe aspirin, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and statins to younger patients and those with more risk factors.

Blood pressure lowering, especially with ACE inhibitors, convincingly improves kidney function and reverses or slows the progression of microalbuminuria, a powerful predictor of CAD.³⁸ Although several large clinical trials in patients with T2D have demonstrated benefits of ACE inhibitors, β -blockers, and diuretics on CVD outcomes, no prospective study or clinical trial has to date reported similar benefits in T1D patients. Current recommendations for all diabetic patients include maintaining diastolic blood pressure <80 mm Hg and systolic blood pressure <130 mm Hg, but some suggest an even lower target for systolic blood pressure, such as <120 mm Hg.³⁹

3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) for lowering cholesterol reduce CAD events in diabetic patients, but almost all study participants have T2D.^{40,41} Nevertheless, clinical practice for prevention of CAD in T1D recommends stringent control of LDL cholesterol. T1D patients often have average or below-average lipoprotein levels but qualitative abnormalities in the composition of lipoproteins. In the Heart Protection Study, treatment with HMG-CoA reductase agents reduced vascular disease in the diabetic cohort, which include \approx 600 T1D subjects.⁴⁰ Although these results were not statistically significant in the T1D subjects (probably because of low power), the magnitude of the reduction in vascular events appeared similar in T1D and T2D. Recommendations for control of LDL cholesterol levels are derived largely from studies in patients with type 2 diabetes⁴⁰ and specific data for type 1 patients are limited. Currently, the Adult Treatment Panel III of the National Cholesterol Education Program already identifies diabetes as a high-risk condition, even in the absence of coronary heart disease. For patients with diabetes and LDL \geq 100 mg/dL, drug therapy is recommended to achieve target-goal levels of $<$ 100 mg/dL. Lower LDL target levels of $<$ 70 mg/dL for diabetic patients with CVD, however, might be an optional goal.⁴²

Importance of Surrogate End Points for Design of Trials to Prevent CAD in T1D

Obstacles to a more widespread use of the aforementioned interventions in primary prevention of CAD in T1D patients include lack of clinical trial data demonstrating safety and long-term efficacy. T1D has a pathophysiology distinct from T2D, and the results of clinical trials in T2D patients may be of limited value. Use of newer techniques to monitor subclinical CAD in addition to clinical end points would lower the sample size and duration requirements. For clinical trials, for this strategy to be acceptable, the sensitivity and positive predictive value of surrogate end points need to be established in the T1D population.

Silent ischemia is common. Twenty-four percent of asymptomatic T1D patients $>$ 35 years have ischemia on exercise test, Holter monitoring, or dynamic perfusion scintigraphy. In addition, 10% have coronary stenosis $>$ 50% when measured by angiography.⁴³ Small clinical studies with B-mode imaging of carotid arteries have suggested that T1D patients have IMT as early as 10 years of age and in relation to diabetes duration.⁴⁴ CAC is an active process often associated with atherosclerotic plaque evolution. Several T1D studies have demonstrated age-specific rates of CAC and associations with a number of classic and emerging CVD risk factors.^{22,37} However, data to date have not established that CAC predicts atherosclerotic events as robustly as ultrasonic assessment of carotid IMT.

In summary, the existing observational studies may provide additional information concerning rates of clinical events, rates of surrogate end point progression, and their relevance to clinically significant disease. Risk factor patterns, including genetic interactions, require further elucidation. Population-based data sources should yield estimates of awareness, treatment, and control of major CAD risk factors in the general population of T1D patients. Future efforts to prevent CAD in

T1D should consider different strategies for primary prevention (in children and young adults with no CAD but increased coronary plaque burden), secondary prevention (in adults with minimal CAD), and tertiary prevention (in patients with advanced CAD and/or end-stage renal disease). Surrogate end points, in addition to clinical end points, should be considered for efficiency reasons and used to shed more light on the pathophysiology of CAD in T1D.

Recommendations

The Working Group participants recommended that the NHLBI and NIDDK provide support to programs that will advance our understanding of CVD and its development in T1D, with the goal of identifying targets for intervention to reduce the occurrence and clinical impact of CVD. The following specific recommendations were made:

- Support mechanistic studies that focus on the vessel wall, endothelial dysfunction, and the role of inflammation in the onset and progression of cardiovascular complications in T1D.
- Expand our understanding of the natural history and clinical course of CVD in T1D, focusing on the development of reliable biomarkers of CVD. Large, clinical databases, such as the EDIC study, may be particularly useful in this regard.
- Support data analyses and evaluate outcomes relevant to CVD from clinical trials in T1D.
- Support registries, such as the CDC SEARCH registry, and expand to other ongoing studies.
- Encourage the development and validation of newly developed imaging methods that could be used in T1D to document the development and progression of CVD.
- Support clinical ancillary studies related to CVD in existing T1D cohorts.
- Use biomarkers and imaging techniques to measure CVD outcomes, and design small, efficient clinical trials to identify new interventions for CVD in T1D.

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