Type 1 Diabetes and Coronary Artery Disease

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Although the increased risk of premature heart disease in type 1 diabetes has been recognized for some time, the underlying pathogenesis is still poorly understood. The most likely factor, a priori, to account for this increased risk is hyperglycemia. However, despite recent evidence from the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study that prior intensive glycemic control reduces cardiovascular disease (CVD), the epidemiologic association between glycemia and coronary heart disease (CHD) is surprisingly weak. This paradox is a focus of the current review, which also evaluates other major determinants of coronary artery disease (CAD) in type 1 diabetes, including the roles of insulin resistance, cytokines, inflammatory biomarkers, and, briefly, genetic factors. Finally, the clinical implications of this information are discussed.

THE MAGNITUDE OF THE PROBLEM

— A high occurrence of, and mortality from, CHD in type 1 diabetes has been documented since the late 1970s (1,2). A 1984 registry reported a 10-fold or greater CHD mortality compared with that expected from U.S. national data (3). This very high relative risk, partly reflecting the extremely low CHD death rate in the general young-adult population, was subsequently confirmed by Joslin investigators (4), who reported that those with type 1 diabetes by 55 years of age experienced a sixfold greater cumulative CHD mortality compared with the rate expected using Framingham Study data. The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) also reported a standardized mortality ratio (SMR) from ischemic heart disease of 9.1 (for men) and 13.5 (for women) for those with a diabetes diagnosis before 30 years of age (5).

Two recent prospective epidemiologic studies, the Pittsburgh Epidemiology of Diabetes Complications (EDC) study (6) and Eurodiab (7), a multicenter, clinic-based study in Europe, confirmed these earlier reports and reported an incidence of total coronary events (including electrocardiogram [ECG] changes) of 16% over 10 years and 9% over 7 years, respectively, of follow-up in type 1 diabetic patients. As the mean age at baseline was ~30 years, these incidence rates reflect the experience of those aged in their late 30s. In EDC, total CAD incidence (including angina and ischemic ECG changes) was >2% per year for those aged ≥35 years. A more recent report (8), using 12-year follow-up data, suggested annual major CAD event (myocardial infarction [MI], fatal CAD, or revascularization) rates of 0.98% for those with diabetes durations of 20–30 years (aged, on average, 28–38 years). These event rates are the same for both sexes, indicating a loss of the protection from CHD mortality that females without diabetes experience.

The Diabetes Epidemiology Research International study will provide an international perspective, comparing cause-specific mortality rates using standard methodologies from representative cohorts of childhood-onset type 1 diabetes in the U.S. (Allegheny County) with national registries of similar individuals in Japan and Finland. CVD was a relatively rare cause of death in the early years of follow-up of these young subjects (9). However, a recent pooled analysis of the Allegheny County and the Pittsburgh EDC cohorts (mean age at follow-up 31 years) demonstrated that CAD was the new leading cause of mortality (10).

The recent follow-up of the Diabetes U.K. (11) cohort of 23,751 subjects diagnosed at <30 years of age with insulin-treated diabetes also shows similar mortality rates for men and women and enables robust sex-specific estimates of SMRs. In those aged 20–29 years, SMRs for ischemic heart disease mortality of 11.8 in men and 44.8 in women were reported, while for those aged 30–39 years, SMRs were 8.0 and 41.6, respectively. Other forms of CVD such as hypertension, valvular disease, cardiomyopathy, heart failure, and stroke were also increased. Whether there has been any recent decline in mortality or morbidity from CHD in type 1 diabetes, as has been reported for renal disease (12,13), is unclear. The Pittsburgh EDC (8) reported no difference in the cumulative incidence of CAD by 20, 25, or 30 years' duration according to year of diagnosis (1950–1980). In contrast, major declines were seen for mortality and renal failure. The benefits of improved diabetes care, therefore, do not (at least as yet) appear to have reduced CAD mortality.

In addition to the above-mentioned studies, which directly deal with CAD events and are summarized in the online appendix Table 1 (available at http://care.diabetesjournals.org), data concern-

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Additional information for this article can be found in an online appendix at http://care.diabetesjournals.org.

Abbreviations: ACS, acute coronary syndrome; ADA, American Diabetes Association; AHA, American Hearth Association; ApoA-IV, Apolipoprotein A-IV; CAC, coronary artery calcification; CAD, coronary artery disease; CHD, coronary heart disease; CVD, cardiovascular disease; DCCT, Diabetes Control and Complications Trial; ECG, electrocardiogram; EDC, Epidemiology of Diabetes Complications; EDIC, Epidemiology of Diabetes Interventions and Complications; eGDR, estimated glucose disposal rate; IL, interleukin; IMT, intima-media thickening; MI, myocardial infarction; SMR, standardized mortality ratio; TNF, tumor necrosis factor; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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ing a variety of other related measures have also been reported (online appendix Table 2). Eleven years after the close of the trial, the former DCCT intensive therapy group showed a lower rate of progression of intima-media thickening (IMT) (14), although glycemic control was similar in both groups after study close. This observation provides the foundation for the "imprinting" theory of glycemic control, i.e., that early vascular changes can lead to fundamental, perhaps structural, alterations that have long-lasting effects.

The excess coronary artery calcification (CAC) in type 1 diabetes seen in studies from Denver (15) and London (16), compared with general nondiabetic control populations, provide further support to the thesis of accelerated atherosclerosis in the coronary arteries. A major concern, however, is whether the calcium reflects atherosclerosis or medial wall calcification (i.e., Mockenberg's sclerosis) commonly seen in type 1 diabetes. The Pittsburgh EDC study provides some reassurance that CAC reflects atherosclerosis, as there was a strong correlation between CAC and both clinical disease and cardiovascular risk factors (17). These three research groups have formed a collaboration to examine the role of electron beam computed tomography in type 1 diabetes. Online appendix Table 3 gives the pooled prevalence of any CAC in the pooled dataset as background for interpreting CAC scores in the type 1 diabetic population. Overall, the risk of having any CAC appears to be increased by ~50%.

Finally, a number of angiographic and autopsy studies further suggest more extensive disease in type 1 diabetic than in nondiabetic cohorts (18–20), as does a study from Oslo (21) that demonstrated, using intravascular ultrasound, that all 29 type 1 diabetic subjects studied had significant coronary intimal thickening. Coincident with changes in IMT are changes in arterial compliance and distensibility. Endothelial dysfunction has been seen in teenage subjects within the first decade of type 1 diabetes onset (22,23). Thus, these studies confirm that changes in vascular structure and function occur early in the course of type 1 diabetes.

RISK FACTORS FOR CAD IN TYPE 1 DIABETES

— When considering CAD risk factors in type 1 diabetes, three major questions arise. First, do the standard CAD risk factors operate as in the nondiabetic population? Second, are there additional specific CAD risk factors in type 1 diabetes? Third, does either (or both) of the above explain the excess risk for CAD?

Online appendix Table 4 summarizes the results that address the first question. In the 10-year follow-up report from EDC, lipids (both HDL and non-HDL cholesterol), hypertension, smoking, and a marker of inflammation, i.e., total white blood cell count, predicted total CAD events with some variation according to the type of CAD event (e.g., depressive symptomatology predicted angina, whereas nephropathy and a proxy measure of insulin sensitivity [estimated glucose disposal rate, eGDR] predicted hard events). eGDR is a regression equation with terms for waist-to-hip ratio, hypertension, and HbA1 and was derived from an hyperinsulinemic-euglycemic clamp substudy of 24 EDC participants. The R^2 for eGDR versus measured GDR was 0.63 (24). Earlier sex-specific analyses (25) suggested that nephropathy was a particularly strong CAD risk factor in men, whereas waist-to-hip ratio and hypertension predominated in women. Intriguingly, glycemic control was not a predictor of CAD, either as a baseline predictor (6) or using a cumulative glycemic exposure measure (26).

Eurodiab, with an 8-year follow-up, largely confirmed these findings, although sex-specific results differed, with proteinuria being independently predictive of CHD in both sexes and waist-to-hip ratio in men (7). Again, HbA_{1c} (A1C) was not independently associated with either events or left ventricular hypertrophy (27). Case ascertainment varied across studies, with ECG abnormalities responsible for more than half the events in Eurodiab, compared with only 19% in EDC. The WESDR also confirmed these findings, where a more limited range of standard risk factors supplemented with detailed retinal characteristics also predicted CVD events, although nephropathy appeared to confound these associations and emerged as a stronger predictor (28). A1C similarly showed only a weak association with MI (P = 0.08) and no association with angina.

A number of important observations emerge from these data and bear on the second question posed, i.e., specific risk factors in type 1 diabetes. First, nephropathy clearly emerges as a major predictor, as has been recognized for many years (29,30) and repeatedly confirmed (31,32). However, even without nephropathy, CAD rates in type 1 diabetes are still greatly increased (30). Another complication often implicated in CAD risk is autonomic neuropathy (33–35). In patients with long-standing type 1 diabetes, the response of myocardial blood flow to sympathetic stimulation, as assessed by a variety of methods, is impaired in myocardial regions with autonomic dysinnervation, indicating impaired vasodilator response of coronary resistance vessels. Perturbations of the autonomic nervous system are, however, strongly associated with renal disease (36), control for which (37,38) may account for much of the high mortality risk associated with autonomic neuropathy, as first noted in Ewing's classic article (34). Numerous mechanisms may account for premature cardiac death in CAD including associations with subclinical but advanced coronary atherosclerosis, abnormalities in coronary vasomotor capacity, changes in systolic and diastolic function, and lastly, life-threatening arrhythmia, the threshold for which is lower in the setting of a relative increase in sympathetic tone, a situation commonly seen in diabetic individuals with sympathovagal imbalance.

Another possibility that may contribute to the enhanced CAD risk in type 1 diabetes is that the effects of standard risk factors are altered. For example, although HDL cholesterol inversely predicts CHD mortality in type 1 diabetes, as in the general population, HDL cholesterol levels are generally ~10 mg/dl higher in type 1 diabetes, probably reflecting a number of factors including enhanced lipoprotein lipase and reduced hepatic lipase activity due to systemic insulin administration and altered HDL metabolism (39). Intriguingly, in a nested case-control study from the Pittsburgh EDC using nuclear magnetic resonance technology, the intermediate (H_3) fraction was increased in those with subsequent CAD compared with noncases (40), while the large (H_4 and H_5) fractions were protective, as in the general population. A lower paraoxonase activity, compromising HDLs ability to retard LDL oxidation, has also been proposed (41).

As shown above, the most logical explanation for the high-CAD risk, hyperglycemia, has in virtually all studies shown only a weak relationship with CAD events. One exception is a small study (42) of older-onset type 1 diabetic Finnish subjects without nephropathy, which is discussed later. Further exploration of the Pittsburgh EDC and WESDR studies

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indicate that glycemia does strongly predict peripheral arterial disease (43), amputation (44), and stroke (28). Why then does glycemia predict the presence and the rate of progression of peripheral, but not coronary, arterial events?

We hypothesize that while glycemia greatly increases atherosclerosis in general, a lower proportion of the plaques formed in diabetic persons are vulnerable. It is rupture of vulnerable plaques that generally leads to coronary events such as MI or CAD death, while plaque rupture has a small role in peripheral arterial disease. This "glucose stabilization" hypothesis would, therefore, predict a stronger relation of glycemia to chronic stable atherosclerotic manifestations (as in occlusive stroke or lower-extremity arterial disease) than to acute coronary events (such as MI and unstable angina) in which plaque rupture is a predominant feature, exactly the epidemiologic pattern seen. A number of observations support this concept. These include the general observation that diabetes complications in other locations, such as the kidney (glomerulosclerosis), eye (fibrous proliferative disease), and joints and connective tissue (stiff joint syndrome), involve a sclerosing or thickening process. This most likely results from glycoxidation of tissue with advanced glycation end product formation and protein cross linking (45). Why should the arterial tree be immune to this aspect of diabetes?

Furthermore, in diabetes, diffuse coronary disease reflecting a greater proportion of concentric lesions (46) and maladaptive remodeling (47) is a common finding that may lead to lumen reduction with a lower frequency of more vulnerable "eccentric" plaques (46,48). Another consistent observation is the complete reversal in the proportion of the two key precipitating factors for acute coronary syndrome (ACS) events in diabetes, namely plaque rupture and plaque erosion. Whereas in the general population ACS is generally precipitated by rupture, in diabetes ACS is much more likely to be precipitated by erosion (49–51). Online appendix Table 5 lists the morphologic studies that provide relevant data. Though the main conclusion is that many morphological features of plaque in diabetes, especially type 1 diabetes, are consistent with a greater tendency toward plaque stability (e.g., ↑ fibrous content, ↓ cell/macrophage/lipid content, and ↑ concentric, ↓ eccentric location of lesions), two important studies suggest that carotid and coronary plaques taken from type 2 diabetic patients undergoing coronary atherectomy (52) or carotid endarterectomy (53) have more inflammatory characteristics than those from matched nondiabetic subjects. A recent postmortem study also suggests greater inflammatory cell infiltration in coronary plaques in diabetes (54). As many of these studies have selection biases, e.g., are event or procedure driven and therefore unlikely to represent the nature and distribution of atherosclerotic lesions in the total diabetes population, a detailed investigation of the morphology of plaque in type 1 diabetes, using representative diabetic and nondiabetic populations, is clearly needed.

In contrast to the relatively weak observational association between glycemia and coronary events, the DCCT/EDIC has recently reported (55), in a 17-year follow-up of the DCCT, that intensive insulin therapy during the 6-year trial was associated with a 42% lower risk of any cardiovascular event and a stunning 57% reduction in major CVD events (stroke, MI, or CAD death) compared with the conventional group. This was despite the two groups having almost identical glycemic control in the 11 years following the trial. This effect of intensive insulin therapy can be largely explained in statistical models by the mean A1C during the DCCT phase.

RECONCILING THE DCCT/EDIC TRIAL DATA WITH PRIOR EPIDEMIOLOGIC OBSERVATIONS

— There are a number of possible reasons why the epidemiologic data are consistently negative in terms of a strong relation of glycemia with CAD risk, whereas the DCCT/EDIC trial results are convincingly positive, all of which may contribute to this paradox (online appendix Table 6).

First, the epidemiology studies may simply be wrong, perhaps because glycemia is based on a single A1C measure. This does not, however, apply to the EDC data, which include a cumulative measure (26). It is also striking that single measures of 25 other risk factors were all significant predictors, whereas HbA1 was not. While a number of studies do suggest a relationship between glycemia and various surrogate markers of atherosclerosis, only one small study ($n = 177$) of older-onset (>30 years) type 1 diabetic subjects without nephropathy reports a link with events (42). Two reports showed A1C/carotid IMT relationships (56,57), whereas an intriguing study from the Turku PET Centre showed a relationship between lifetime (but not concurrent) glycemic exposure and coronary vasoreactivity (58). Chan et al. (59) also suggested that poorer control may be related to lower acetyl choline–stimulated nitric oxide production. Though two studies have shown poorer left ventricular function in those with poor glycemic control (60,61), two others have shown no association between angiographic findings and A1C (20,62). Both the intravascular ultrasound–determined coronary intima thickening that was omniprevalent in type 1 diabetic subjects in the Oslo study (21) and coronary plaque development were correlated with mean 18-year A1C levels ($P = 0.04$). These studies, using surrogate markers rather than clinical events, are thus not inconsistent with the above glucose stabilization hypothesis, nor with the epidemiology studies based on clinical events.

Population characteristics also differ between the DCCT and the EDC/WESDR/Eurodiab studies. Particularly notable is the relatively shorter diabetes duration of DCCT/EDIC subjects at baseline (mean 6 years) compared, for example, with a mean of 19 years for EDC and 14 years for Eurodiab. It thus seems likely that the DCCT/EDIC hypothesis of the benefits of early imprinting may be particularly relevant. Another difference is the low CAD risk of the DCCT population resulting from the exclusion of obese, hypertensive, and hypercholesterolemic subjects at baseline. The DCCT/EDIC results are thus derived from a relatively healthy, compliant, early onset, low CVD risk subgroup of the type 1 population, features that may contribute to the differences under discussion.

Another potential contributor is the lower level of glycemic control achieved in the DCCT/EDIC intensive group (A1C 7.4% compared with 9.1% in the conventional group), which suggests that the benefit of improved glycemic control may only occur if sufficiently low levels are achieved. Yet another potential explanation is that the DCCT/EDIC trial data reflect other factors beyond improved glycemic control; thus, the ability of mean DCCT A1C to explain the treatment group effects may reflect how good a marker it is of being in the intensive therapy group rather than glycemia per se. A major reduction in the DCCT treatment group effect occurred after controlling for

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microalbuminuria or worse (*P* value increased from 0.005 to 0.04) (55). In EDC, 71% of incident CAD cases had microalbuminuria or worse at baseline, and a further 11% developed microalbuminuria at or before the first CAD event, suggesting that 80% of events may be associated with renal disease. Unfortunately, the frequency of developing microalbuminuria or worse before CAD is not reported for DCCT/EDIC, making it difficult to fully quantify the impact of early renal disease on CAD risk in DCCT/EDIC. Apart from renal disease, other factors may have contributed but have not yet been included in multivariable analyses. For example, though LDL cholesterol at the end of DCCT was not different between the groups, during the trial, total and LDL cholesterol and triglycerides were all lower ($P < 0.01$) in those receiving intensive therapy.

It would thus seem, given the population differences, the lower A1C levels achieved in the DCCT, and the current incomplete adjustment for potential mediators of the treatment group effect, that the paradox may not be so puzzling after all. As >80% of CAD in type 1 diabetes may be associated with renal disease in general cohorts and insulin resistance is a strong predictor of both CAD (6) and renal disease (63), insulin resistance is likely the major pathogenetic pathway for the majority of cases. The potential importance of insulin resistance is further underscored by the observations that a family history of type 2 diabetes predicts CAD in type 1 diabetes (64) and that a subgroup of type 1 diabetic subjects gain excessive weight, show insulin resistance, and have adverse lipoprotein changes when given intensive insulin therapy (65,66). Thus, a subgroup of type 1 diabetes may have type 2 diabetes/insulin resistance genes and be at increased CAD risk. Nonetheless, glycemia per se may particularly relate, as the Finnish data suggest (42), to the nonrenal CAD cases, which are likely to be more predominant in the DCCT because of the lower risk of renal disease resulting from better glycemic control.

NOVEL PREDICTORS — Over the past decade, atherosclerosis has increasingly been considered, at least partly, an inflammatory disease (67). Several newly recognized factors may contribute to this development and are discussed below (45,67–69).

The oxidative modification of LDL, and the immune response it produces, may be one of these key factors, as an association between antibodies to oxidized LDL and incident CAD has been reported (70). The resulting immune complexes may induce foam cell formation and damage the endothelium (71), activating macrophages and endothelial cells and impairing the physiologic action of nitric oxide, leading to vascular cell cytotoxicity (67,72). The adherence of monocytes is also a key step in this process (67,73), and it is of interest that E-selectin shows a strong, independent prediction of heart disease in type 1 diabetes (74).

Other regulators of adhesion molecules include cytokines, such as tumor necrosis factor-α (TNF-α), interleukin (IL)-6, and IL-1β (75). These and other markers of inflammation have not been extensively studied in the development of CAD. However, the Eurodiab study group, using a *Z* score based on combined levels of C-reactive protein, IL-6, and TNF-α (76), reported a significant difference between those with and without CAD ($P < 0.001$) after adjustment for age, sex, A1C, diabetes duration, and systolic blood pressure. In further reports, no cross-sectional association between homocysteine concentration and CVD was seen in Eurodiab (77), while the EDC study failed to show any independent prediction of CAD by plasminogen activator inhibitor-1 or tissue plasminogen activator inhibitor-1 (78). In contrast, soluble IL-2 receptor, a marker of T-cell activation, has been associated with progression of CAC in type 1 diabetes (79). Additionally, increased CD40 ligand expression and upregulation of soluble CD40 ligand have been reported in type 1 diabetes (80,81) and appear to play a role in endothelial cell activation and monocyte recruitment.

The adipokine adiponectin, one of the most abundant circulating proteins in human plasma (82), which preferentially accumulates in the subintimal space of the arterial wall when the vascular endothelium is injured, has received much attention (83). It inhibits TNF-α–induced cell adhesion in human aortic endothelial cells and expression of cellular adhesion molecules in a dose-response manner (84) and may act both as an antiatherogenic and an anti-inflammatory molecule. Studies in type 1 diabetes are limited and confusing because despite the high rates of atherosclerosis, markedly elevated adiponectin concentrations have been observed in type 1 diabetes compared with both type 2 diabetes and normal glucose tolerance (85,86). Since insulin is implicated in the regulation of adiponectin expression (87), the relatively high systemic levels of insulin in type 1 diabetes may play a role. Higher rates of macroalbuminuria in the type 1 populations examined may also contribute, as increased adiponectin concentration has been noted in renal disease (88–90). Nevertheless, a remarkable 63% lower CAD risk per 1 SD (6.3 μg/ml) increase in serum adiponectin concentration has been reported among type 1 diabetic individuals in the EDC study (90) after adjustment for traditional risk factors, including urinary albumin excretion. Investigators from the Coronary Artery Calcification in Type 1 Diabetes (CACTI) study have also reported that low plasma adiponectin levels were independently associated with greater CAC progression in type 1 diabetes (91). However, whether the high levels in type 1 diabetes (or renal disease) reflect an attempt to counteract the atherogenicity of the condition, or are merely reflective of this state, remains unclear.

GENETIC STUDIES — A number of studies have demonstrated a familial effect on CVD risk in general and in type 1 diabetes (64,92,93). However, only a few studies (online appendix Table 7) have focused on a genetic predisposition to CAD in type 1 diabetes.

Receptor for advanced glycation end products

Receptor for advanced glycation end products, located on chromosome 6p21.3 in the class III region of the major histocompatibility complex and an important locus for type 1 diabetes pathogenesis, is involved in key mechanisms leading to vascular disease development during chronic hyperglycemia (53,94,95). The AA genotype at position −374 of the promoter region has been associated with lower CVD risk in type 1 diabetes compared with the TT + TA genotypes (96), and in type 2 diabetes and the general population as well (97,98).

ACE insertion/deletion polymorphism

This polymorphism accounts for a large proportion of the individual variation of serum and tissue ACE activity (99,100) and contributes, in some reports, to the risk of persistent microalbuminuria/

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severe nephropathy in type 1 diabetes (101,102). The association of this polymorphism with CAD is complex and inconsistent, with the ACE II genotype being reported to have a significantly lower MI risk in one (103) but not all (104) studies. The situation is further complicated by the associations of the I-allele with insulin resistance (105) and the D-allele with nephropathy, the major risk factor for CAD in type 1 diabetes (106).

Neuropeptide Y

A leucine to proline polymorphism (Leu7Pro) of the neuropeptide Y gene localized on chromosome 7p15.1 may contribute to the genetic susceptibility to CHD in type 1 diabetes, possibly by influencing glycemic control and lipid metabolism (107,108). However, the association with A1C was not confirmed in another recent nondiabetic study (109).

Hepatic lipase

The hepatic lipase gene promoter polymorphism −480C/T (or −514C/T, depending on identification of transcription start localization), a functional variant influencing hepatic lipase activity (110), has been associated with a higher frequency of CAC independent of HDL cholesterol in type 1 diabetes (111) and premature CHD (112,113), as well as CAC (114), in a variety of populations. Intriguingly, reports of higher CAD risk and lower HDL concentrations among those with the −480C rather than the −480T allele also exist (115,116). The LIPC −480C/T polymorphism has been recently associated with insulin resistance (117,118).

Apolipoprotein A-IV

Apolipoprotein A-IV (ApoA-IV) is a structural glycoprotein of chylomicrons, HDL, and VLDL and plays an important role in the reverse cholesterol transport from peripheral cells to the liver (119). A common polymorphism (glutamine to histidine at position 360 near the carboxyl terminus) generates two isoforms, apoA-IV1 (360Gln) and apoA-IV2 (360His). The latter has been associated with a significantly higher risk of subclinical CAD progression (relative risk 3.3, $P = 0.003$) in type 1 diabetic patients (120) and MI in type 2 diabetic patients (121) but not in nondiabetic control subjects (120).

Von Willebrand factor

The Von Willebrand factor Thr789Ala polymorphism has been associated with increased CHD risk among type 1 diabetic patients with long diabetes durations (odds ratio 4.2 for Ala/Ala homozygotes) (122). Von Willebrand factor, a carrier of coagulation factor VIII, has been identified as a risk factor for MI in the general population (123).

Further exploration of the genetic basis of CAD in type 1 diabetes

Research to date has shown a number of promising avenues to further explore the relationship between genes and CAD in type 1 diabetes, particularly in the realm of specific gene-environmental interactions. Future research might reasonably focus on genes not having a proatherogenic effect or those mildly associated with CAD in nondiabetic populations that become strongly "activated" in the diabetes milieu, e.g., genes associated with glucose metabolism and/or insulin resistance. Adiponectin would also be of particular interest, given the growing evidence that genetic variants of the *APM1* gene (11391G/−11377G haplotype T45G, G276T) affect adiponectin levels and are associated with cardiovascular risk in type 2 diabetes and nondiabetic control subjects (124–126) and nephropathy in type 1 diabetes (127).

CONCLUSIONS AND CLINICAL IMPLICATIONS

It is clear that type 1 diabetes is associated with an increased risk for CHD and that this risk is evident at a young age. Underlying this enhanced risk is a wide range of modifiable risk indicators such as standard CAD risk factors (blood pressure, lipids, and smoking), as well as specific elements such as renal disease. The relation of glycemia to clinical events is multifactorial and complex. Unfortunately, clinical trial data specific to type 1 diabetes and CAD prevention are largely limited to the DCCT/EDIC study, which suggests a very strong benefit for early, intensive glycemic management, although to what degree this finding is mediated via other pathways (e.g., lipids) is currently unknown.

There are few outcome data on primary prevention of CHD in type 1 diabetes, and current guidelines in type 1 diabetic patients mirror those established for type 2 diabetes. The Heart Protection Study (128) suggested a benefit of simvastatin in the type 1 diabetic subgroup (128). In general, we must infer that the benefits of pharmacotherapy for CHD prevention as established in numerous trials in the general and type 2 diabetic populations would apply equally to type 1 diabetes. Highlights of current American Diabetes Association (ADA) (129) and American Heart Association (AHA) (130,131) recommendations are summarized in online appendix Table 8. Both the ADA and AHA advocate moderately vigorous lipid and blood pressure control and even initiating drug therapy in childhood if medical nutrition therapy has failed to reduce LDL cholesterol to <160 mg/dl (or <130 mg/dl in the presence of an adverse CVD risk profile). Similarly, blood pressure should be treated with drugs if consistently >95th percentile or 130/80 mg/dl, whichever is lower. These strong recommendations are to be encouraged, especially as adequate blood pressure and lipid awareness and control is low in the type 1 diabetic population (132,133). Both organizations also provide extensive discussion of these issues as they apply to youth (131,134), although specific age cutoffs for drug therapy have not been firmly established. What is evident, however, is that a greater number of CHD risk factors accumulate in type 1 diabetic persons at an early age, such that many of them may qualify for risk factor intervention by the time they reach 25 years of age (135). In addition, more young people today are overweight and obese, and the development of insulin resistance with its associated atherogenic risk factors in type 1 diabetes may further increase the CHD risk.

The role of screening for CAD in diabetes has been debated for many years. To assess candidacy for renal transplantation in type 1 diabetic patients, screening is not debated, as up to 50% of these patients have asymptomatic significant CAD (136). The AHA Prevention VI Conference (130) suggested that noninvasive testing may be useful for management in type 1 diabetes but acknowledged that there were no evidence-based recommendations. A 1998 ADA consensus development conference also provided a categorization of high-risk subjects in whom screening might be considered appropriate. Recommendations for selection of testing modality were also made (137). Recent data suggest that the criteria put forth by the 1998 ADA conference are not predictive as to who will have CAD when screened (138). Given that CHD is a major cause of death in type 1 diabetes,

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more studies are needed to investigate the proper role of screening and whether new imaging modalities such as computed tomography angiography should change our approach to the patient with type 1 diabetes. Meanwhile, clinician and patient are urged to minimize cardiovascular risk by rigorous glycemic, lipid, and blood pressure control.

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