Coronary Artery Disease Is Common in Nonuremic, Asymptomatic Type 1 Diabetic Islet Transplant Candidates

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OBJECTIVE — Coronary artery disease (CAD) is the most common cause of death in patients with type 1 diabetes. Asymptomatic CAD is common in uremic diabetic patients, but its prevalence in nonuremic type 1 diabetic patients is unknown. The prevalence of CAD was determined by coronary angiography and the performance of noninvasive cardiac investigation evaluated in type 1 diabetic islet transplant (ITX) candidates with preserved renal function.

RESEARCH DESIGN AND METHODS — A total of 60 consecutive type 1 diabetic ITX candidates (average age 46 years [mean 24–64], 23 men, and 47% ever smokers) underwent coronary angiography, electrocardiographic stress testing (EST), and myocardial perfusion imaging (MPI) in a prospective cohort study. CAD was indicated on angiography by the presence of stenoses >50%. Models to predict CAD were examined by logistic regression.

RESULTS — Most subjects (53 of 60) had no history or symptoms of CAD; 23 (43%) of these asymptomatic subjects had stenoses >50%. CAD was associated with age, duration of diabetes, hypertension, and smoking. Although specific, EST and MPI were not sensitive as predictors of CAD on angiography (specificity 0.97 and 0.93, sensitivity 0.17 and 0.04, respectively) but helped identify two of three subjects requiring revascularization. EST and MPI did not enhance logistic regression models. A clinical algorithm to identify low-risk subjects who may not require angiography was highly sensitive but was applicable only to a minority ($n = 8$, sensitivity 1.0, specificity 0.27, negative predictive value 1.0).

CONCLUSIONS — Nonuremic type 1 diabetic patients with hypoglycemic unawareness and/or metabolic lability referred for ITX are at high risk for asymptomatic CAD despite negative noninvasive investigations. Aggressive management of cardiovascular risk factors and further investigation into optimal cardiac risk stratification in type 1 diabetes are warranted.

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Type 1 diabetes is associated with a more than threefold increase in mortality compared with that in the general population, mainly due to cardiovascular disease (1). Clinical assessment and management of this high-risk population are challenging because they frequently have multiple cardiovascular risk factors, suffer from comorbid diseases, and may lack typical symptoms of ischemia (silent myocardial ischemia and infarction).

Islet transplantation (ITX) can cure hypoglycemia and stabilize glycemia and may be indicated for type 1 diabetic patients with severe hypoglycemia (usually with hypoglycemia unawareness) and metabolic lability despite optimal therapy (2). The nephrotoxicity of immunosuppressants excludes those with significant renal impairment. Most ITX candidates have long-standing diabetes and many have neuropathy. Diabetes per se, a long duration of diabetes (3), and autonomic neuropathy (4) are risk factors for coronary artery disease (CAD), which may be asymptomatic (5–7). Furthermore, the long-term impact of ITX on CAD is unknown.

Current data indicating a high prevalence of CAD (both clinically manifest and asymptomatic) and evaluating the performance of noninvasive cardiac investigations to identify significant CAD in this population seem less than optimal. Because end-stage renal disease itself is associated with excess cardiovascular morbidity and mortality (8), it is unclear whether data from diabetic patients being assessed for renal transplantation can be extrapolated to ITX candidates. To date, there is a paucity of data regarding the prevalence of CAD and the performance of noninvasive investigations in type 1 diabetic patients with preserved renal function being assessed for ITX.

Although the optimal means are unclear, careful cardiovascular assessment before transplantation seems prudent. Clinical assessment probably underestimates CAD risk because asymptomatic CAD is common in type 1 diabetes (9) and largely independent of conventional risk factors (7).

Although aggressive risk factor reduction is warranted in this population, noninvasive and invasive cardiac investigation before ITX provides an opportunity to determine the degree of CAD and enhance patients' short- and long-term outcomes. Accordingly, the purpose of this study was to assess the degree of CAD and its relationship to clinical and biochemical features and to evaluate the performance of noninvasive investigations in type 1 diabetic pa-

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Abbreviations: ACS, acute coronary syndrome; CAD, coronary artery disease; EST, electrocardiographic stress testing; ITX, islet transplantation; MPI, myocardial perfusion imaging.

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

tients without significant renal impairment during assessment for ITX.

RESEARCH DESIGN AND METHODS

— A total of 60 consecutive C-peptide–negative type 1 diabetic patients undergoing assessment for ITX at the University of Alberta were evaluated. All subjects gave written informed consent, and the research ethics board approved evaluation of these data. Inclusion criteria for ITX at the University of Alberta are 18–65 years of age, type 1 diabetes complicated by severe hypoglycemia, hypoglycemic unawareness, and/or severe metabolic instability despite optimal insulin therapy (10). Exclusion criteria include smoking within the previous 6 months, significant renal impairment (glomerular filtration rate <40 ml/min), malignancy, and weight >90 kg. Subjects with previous CAD were not excluded.

A comprehensive assessment by the islet transplant program's endocrinologists and surgeon, including history and physical examination, was performed in all subjects. Fasting glucose, HbA_{1c}, total cholesterol, HDL cholesterol, LDL cholesterol, triglyceride, homocysteine, lipoprotein(a), and plasma creatinine levels were measured using a Hitachi 917 multichannel analyzer (Roche Diagnostics, Indianapolis, IN). Urinary albumin excretion rate and creatinine clearance were determined from a 24-h urine collection. Glomerular filtration rate was calculated from the clearance of ^{99m}Tc-diethylenetriaminepentaacetic acid and corrected for body surface area. Microvascular complications were determined based on history of laser therapy for retinopathy with laser scars on funduscopy, clinical signs of peripheral sensory neuropathy (reduced perception of 10-g monofilament or reduced vibration, pinprick, or temperature sensation), and history of microalbuminuria or macroalbuminuria with supportive current or historical laboratory values (albumin excretion rate >20 and >200 μg/min, respectively). A clinical diagnosis of autonomic neuropathy was made in patients with orthostatic hypotension (decrease in systolic blood pressure of >20 mmHg) or a history of erectile dysfunction (in the absence of hypogonadism), gastroparesis, or other gastrointestinal dysmotility suggestive of autonomic neuropathy in the absence of any other cause. Determination of the presence of hypoglycemia unawareness was made by the endocrinologist based on history and review of 1 month of home blood glucose monitoring records and written records describing any hypoglycemic events during that period (10).

Cardiovascular assessment, noninvasive myocardial perfusion imaging (MPI), and cardiac catheterization with angiography were performed in all patients. Electrocardiography stress testing (EST) was performed using exercise in most patients (52 of 60), with blood pressure and electrocardiographic monitoring, until target heart rate was attained ($n = 43$), electrocardiogram changes were observed (with fatigue and leg pain, $n = 2$; with no symptoms, $n = 1$), or symptoms developed (exhaustion at a high workload: Bruce stage 4, $n = 6$). In eight patients, EST was performed using dipyridamole because clinical factors precluded exercise. Horizontal or downsloping ST-segment depression of ≥1 mm at 0.08 s beyond the J point indicated a positive result (11). MPI was performed using ^{99m}Tc-sestamibi after exercise alone ($n = 48$), dipyridamole ($n = 8$), or a combination of both ($n = 4$), reflecting routine clinical practice. Reversible perfusion defects on stress imaging indicated a positive result for ischemia with fixed perfusion defects representing myocardial infarction.

Cardiac catheterization results were reviewed by a single experienced interventional cardiologist. Significant CAD was defined as presence of a stenosis in a major coronary vessel >50% of the luminal diameter, because this predicts excess cardiac deaths in diabetic patients evaluated for renal transplantation (12).

Data were analyzed using SPSS version 11 software for Macintosh (SPSS, Chicago, IL). Normally distributed data are presented as means ± SD, and differences were compared using Student's *t* test. Otherwise, medians (range) are presented and compared using a Mann-Whitney *U* test. Proportions were compared using Fisher's exact test (two tailed). Logistic regression was used to develop and test the ability of models to rule out the presence of CAD (i.e., maximize negative predictive value) and examine the impact of the addition of noninvasive testing to the model. Statistical significance was set at 5%.

RESULTS

— The mean age and duration of diabetes were 45.8 years (range 24–64) and 30.7 years (10–52), respectively, and 23 patients (38.3%) were men. Most subjects had significant hypoglycemia unawareness (87%), and a clinical diagnosis of autonomic neuropathy was made in 30% of subjects. The clinical and biochemical characteristics of the subjects, including the clinical features of subjects with or without a history of CAD, are presented in Table 1.

Most subjects (53 of 60, 88%) had no history or symptoms of CAD. Seven patients had a history of CAD: angina with positive MPI (one patient), hospital-diagnosed myocardial infarct (three patients), or positive angiogram (three patients). The presenting symptoms in these patients were angina (one patient), atypical chest pain (three patients), or acute coronary syndrome (ACS) (three patients). Nonspecific T-wave abnormalities were present in 3 of 53 asymptomatic subjects and in 4 of 7 patients with known CAD.

Compared with asymptomatic subjects, those with history of CAD were older and more likely to report antihypertensive therapy or use of aspirin or β-blockers but had lower total cholesterol and LDL cholesterol levels (categorized as "Known CAD" in Table 1). Duration of diabetes, sex, smoking history, current blood pressure, HbA_{1c}, renal function, microvascular complications, or use of statins or ACE inhibitors/angiotensin II receptor antagonists did not differ.

Coronary angiography

Significant CAD was present in 23 patients (43%) and minor CAD (<50% stenosis) was present in 7 of the 53 asymptomatic subjects (Fig. 1). Single-vessel disease was present in 13 patients, two-vessel disease was present in seven patients, and three-vessel disease was present in three patients. The presence of CAD was confirmed by angiography in all seven subjects with a history of CAD. One patient had undergone coronary artery bypass grafting with well-functioning grafts, and one patient had undergone angioplasty to the left anterior descending artery with no significant residual stenosis. One subject was deemed unsuitable for ITX due to severe three-vessel CAD that was not amenable to intervention.

Relationship between risk factors and presence of significant CAD on angiography in asymptomatic subjects

The clinical and biochemical characteristics of asymptomatic subjects with and

Table 1—*Clinical and biochemical characteristics of ITX candidates as a whole and subdivided into known cases of CAD and asymptomatic subjects with or without significant CAD on angiography*

	All subjects	Known CAD	Asymptomatic		*P**
			CAD	No CAD	
n	60	7	23	30	
Age (years)	45.8 ± 9.6	53.0 ± 6.3†	48.8 ± 9.4	41.7 ± 8.6	0.006
Duration of diabetes (years)	30.7 ± 10.5	33 ± 10.0	34.6 ± 9.5	27.1 ± 10.6 (10–51)	0.009
Hypoglycemia unawareness	52 (87)	7 (100)	20 (87)	25 (83)	NS
Men	23 (38.3)	3 (42.9)	9 (39.1)	11 (36.7)	NS
BMI (kg/m^2)	24.9 ± 2.6	25.1 ± 1.7	25.2 ± 2.4	24.7 ± 3.0	NS
Systolic blood pressure (mmHg)	137 ± 21.6	134 ± 18.6	145 ± 23.0	132 ± 20.1	0.039
Diastolic blood pressure (mmHg)	75 ± 10.3	72 ± 9.9	73 ± 11.0	77 ± 9.7	NS
Insulin dose (units · kg^{-1} · day^{-1})	0.58 ± 0.17	0.50 ± 0.09	0.53 ± 0.17	0.63 ± 0.17	0.05
Ever smoker	28 (46.7)	5 (71.4)	13 (56.5)	10 (33.3)	0.1
Cigarette exposure (pack-years)	12 (2–30)	5 (2–28)	17.5 (3–30)	6 (2–20)	0.035
Laboratory values					
HbA_{1c} (%)	7.9 ± 1.3	8.2 ± 1.0	7.7 ± 1.2	7.9 ± 1.6	NS
Cholesterol (mmol/l)	4.44 ± 0.79	3.89 ± 0.64†	4.69 ± 0.78	4.38 ± 0.78	NS
LDL cholesterol (mmol/l)	2.54 ± 0.59	2.04 ± 0.42‡	2.72 ± 0.64	2.52 ± 0.52	NS
HDL cholesterol (mmol/l)	1.52 ± 0.34	1.43 ± 0.29	1.55 (0.98–2.27)	1.46 (0.92–2.46)	NS
Triglycerides (mmol/l)	0.71 (0.34–4.2)	1.1 (0.47–4.2)	0.77 (0.34–1.36)	0.60 (0.35–3.20)	NS
Creatinine (μmol/l)	77 (54–118)	74 (66–118)	77 (60–107)	78 (54–96)	NS
Glomerular filtration rate (ml/min)	90 (42–131)	75 (46–106)	84 (42–131)	93 (65–115)	NS
Albumin excretion rate (μg/min)	10 (4–570)	7 (5–10)	14 (4–570)	9.5 (5–295)	NS
Lipoprotein a (g/l)	0.12 (<0.03–0.97)	0.21 (<0.03–0.80)	0.11 (<0.03–0.62)	0.14 (<0.03–0.97)	NS
Homocysteine (μmol/l)	7.3 (3.4–77.6)	7.45 (5.9–8.8)	8.3 (5.6–21.8)	6.9 (3.4–77.6)	NS
Drug treatment					
Antihypertensives	21 (35)	5 (71.4)†	11 (47.8)	5 (16.7)	0.019
ACE inhibitor/angiotensin II receptor antagonists	35 (58)	5 (71)	17 (74)	13 (43)	0.049
Aspirin	9 (15)	4 (57.1)‡	3 (13)	2 (6.7)	NS
β-Blockers	3 (5)	3 (42.9)§	0	0	NS
Statins	21 (35)	4 (57)	9 (39)	8 (27)	NS
Microvascular complications					
Laser treatment for retinopathy	30 (50)	4 (57.1)	11 (47.8)	15 (50)	NS
Clinical signs of peripheral neuropathy	23 (38.3)	3 (42.9)	11 (47.8)	9 (30)	NS
History of microalbuminuria or macroalbuminuria	18 (30)	2 (29)	9 (39)	7 (23)	NS
Clinical diagnosis of autonomic neuropathy	18 (30)	3 (43)	7 (30)	8 (27)	NS

Data are means ± SD, *n* (%), or median (range). CAD and no CAD indicate the presence or absence, respectively, of stenoses ≥50% on angiography. *CAD versus no CAD. †$P < 0.05$, ‡$P < 0.02$, §$P = 0.001$ vs. asymptomatic subjects ($n = 53$).

without CAD are compared in the two right columns of Table 1. Subjects with CAD were older, had longer duration of diabetes, had greater cigarette exposure, had higher systolic blood pressure, and were more likely to report use of antihypertensive drugs or ACE inhibitors/angiotensin II receptor antagonists. There were no differences in sex, glycemia, lipid profile, renal function, albuminuria, lipoprotein(a), or homocysteine levels or in reported use of statins or aspirin. No patients were taking β-blockers.

Utility of EST and MPI in asymptomatic subjects

Sensitivity and specificity. Among the 53 asymptomatic subjects, EST was positive for ischemia in five patients, whereas a reversible perfusion defect on MPI was noted in only three subjects. No fixed perfusion defects were observed. The sensitivity, specificity, and positive and negative predictive values of EST and MPI to detect CAD are shown in Table 2.

Logistic regression. A logistic regression model estimating the predictors of CAD on angiography is shown in Table 3. (CAD was the dependent variable: present = 1, absent = 0.) The model was highly significant as a predictor of the presence of CAD ($\chi^2 = 34.32$ with 10 degrees of freedom, $P < 0.001$), correctly

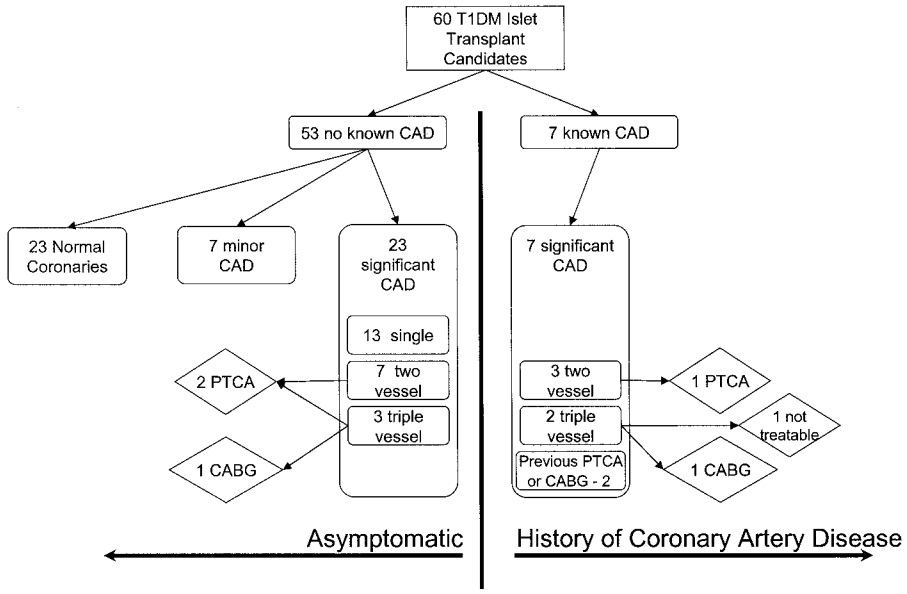

Figure 1—*Angiographic findings and outcomes in 60 consecutive type 1 diabetic ITX candidates. Stenoses >50% of the luminal diameter were considered indicative of significant CAD, and stenoses <50% were considered indicative of minor CAD. CABG, coronary artery bypass grafting; PTCA, percutaneous transluminal coronary angioplasty; T1DM, type 1 diabetes.*

identified 20 of 23 subjects with CAD and had a negative predictive value of 0.9.

Neither a positive result of EST nor a positive result of MPI was an independent predictor of CAD when added to the model. The addition of a positive result of EST to the model was associated with an increased number of false-negative results, although the model remained highly significant. The addition of a positive result of MPI did not improve the model's performance.

Prediction of a low-risk subgroup

An algorithm developed previously in kidney transplantation (13) to identify asymptomatic individuals with diabetes at low risk for CAD was applied to this study population. The algorithm (subjects <45 years of age with duration of diabetes <25 years, normal resting electrocardiogram, and lifelong nonsmoker) identified eight subjects (15%) with low risk. None of these eight subjects had CAD on angiography. Therefore, the sensitivity, specificity, and negative predictive value of the algorithm were 1.0 (95% CI 0.82–1.0), 0.27 (0.13–0.46), and 1.0 (0.60–1.0), respectively.

CONCLUSIONS — Our results show that angiographically significant but clinically silent CAD is common in ITX candidates with long-standing and "difficult" diabetes (frequent hypoglycemia with hypoglycemia unawareness and/or glycemic lability) but preserved renal function. Most cases of CAD were found in asymptomatic subjects, and only a small proportion of ITX candidates were known to have preexisting ischemic heart disease. Even in subjects with preexisting CAD, only one had typical angina, and many had been asymptomatic until presenting with an ACS. This is consistent with observations that ACS is a common presenting feature of CAD in diabetic subjects (14).

These data suggest that significant coronary stenoses may be more common in asymptomatic type 1 diabetic patients in general than previously suspected. It is also clear that clinically silent but significant CAD is not a problem confined to type 1 diabetic patients with end-stage renal disease. In most cases, CAD affected a single vessel, and revascularization was recommended in only three asymptomatic subjects. The high prevalence of angiographically demonstrated CAD is surprising when traditional cardiovascular risk factors are considered. The group was relatively young, and most subjects were women, although in patients with diabetes, female sex is not cardioprotective (15). Furthermore, lipid levels and glycemia, although examined cross-sectionally, were well controlled and did not predict the presence of CAD. Cholesterol levels were lower in the seven subjects with a history of CAD, perhaps reflecting more aggressive statin therapy. Reported use of statins and ACE inhibitors or angiotensin II receptor antagonists was common. The most powerful risk factors for CAD were age, duration of diabetes, hypertension, and smoking.

Many subjects had clinical features (that were probably underestimated) suggesting autonomic neuropathy, and most patients had significant hypoglycemia unawareness, both of which could predispose patients to asymptomatic CAD (16). Compared with age- and duration-

Table 2—*Presence of significant CAD on angiography in asymptomatic subjects undergoing EST and MPI*

	EST positive for ischemia		Reversible perfusion defect on MPI		
	CAD+	CAD−	CAD+	CAD−	Total
EST+	4	1			5
EST−	19	29			48
Total	23	30			53
MPI+			1	2	3
MPI−			22	28	50
Total			23	30	53
Sensitivity	0.17 (0.06–0.04)		0.04 (0.00–0.24)		
Specificity	0.97 (0.81–1.0)		0.93 (0.76–0.99)		
Positive predictive value	0.80 (0.30–0.99)		0.33 (0.02–0.87)		
Negative predictive value	0.40 (0.26–0.55)		0.56 (0.41–0.70)		

Data are *n* or *n* (95% CI).

Table 3—*Logistic regression (dependent variable = presence of significant CAD on angiography)*

	Model 1		Model 1 + EST		Model 1 + MPI	
	Coefficient	*P*	Coefficient	*P*	Coefficient	*P*
Age (years)	−0.11	0.145	−0.13	0.072	−0.12	0.115
Hypertension (present = 1)	4.3	0.016	4.48	0.012	4.88	0.015
Smoker (never = 0)	1.9	0.19	1.20	0.203	2.54	0.136
Pack-years of smoking	0.16	0.069	0.16	0.111	0.16	0.073
Creatinine clearance (ml/min)	−0.039	0.039	−0.052	0.044	−0.041	0.056
BMI (kg/m^2)	0.42	0.042	0.39	0.055	0.46	0.036
Diastolic blood pressure (mmHg)	−0.14	0.015	−0.14	0.017	−0.15	0.016
LDL cholesterol (mmol/l)	2.78	0.026	3.68	0.015	2.88	0.028
Homocysteine (μmol/l))	−0.05	0.219	−0.05	0.178	−0.06	0.179
HbA_{1c} (%)	−1.05	0.045	−1.15	0.029	−1.08	0.043
Positive EST (positive = 1)			4.15	0.21		
Positive MPI (positive = 1)					−2.32	0.28
Model χ^2 (degrees of freedom)	34.32 (10)		37.14 (11)		35.49 (11)	
P	<0.001		<0.001		<0.001	
False negatives	3/23		4/23		3/23	
False-positives	4/30		4/30		4/30	
Negative predictive value	0.90		0.87		0.90	

matched type 1 diabetes control subjects, ITX candidates have more hypoglycemia (10) but lower blood glucose levels (17), which may lower the risk of developing CAD. It is possible that glycemic lability in this population could contribute to increased risk of CAD because postprandial hyperglycemia in impaired glucose tolerance (18) and type 2 diabetes (19) is associated with increased cardiovascular mortality.

There are few prior studies with which the current study can be directly compared. The prevalence of CAD in asymptomatic individuals in this study is more than 10 times higher than in a sample of the general population, even though that population was older (3.8%), (20) and four times higher than that observed at autopsy in cases of noncardiac, sudden death (10%) (21). Coronary artery calcification, a marker of early coronary atherosclerosis, was present in 11% of young adults with type 1 diabetes (mean age 20 years, mean duration of diabetes 12 years) (22). One study has reported CAD in 34% of type 1 diabetic patients of similar age and duration of diabetes as our subjects undergoing angiography (6).

Other studies in asymptomatic diabetic subjects with end-stage renal disease or multiple cardiac risk factors have indicated prevalence rates between 30% (23) and 53% (24), which are comparable with our data. In most studies examining the prevalence of CAD in diabetes, angiography has been performed only in subjects with abnormal results of EST or perfusion scans and, therefore, the prevalence rates may have been underestimated.

The sensitivity of EST and MPI in the current study is much lower than in previous studies. However, most researchers have evaluated symptomatic subjects and generally performed angiography only in subjects with abnormal screening tests (25). Because noninvasive screening tests perform best when the pretest probability of CAD is intermediate, and the number of false-negative results increases as the pretest probability increases (26), the high pretest probability in our subjects will have contributed to the low sensitivity. Although a small number of subjects did not reach target heart rate despite a high workload (probably reflecting autonomic neuropathy), it seems unlikely that insufficient stress explains the low sensitivity of EST.

Although EST and MPI were not good predictors of the presence of CAD, they were specific and assisted in guiding the clinical management of individuals. Only three asymptomatic patients required revascularization. However, in one patient, despite high-risk coronary anatomy (90% stenoses in both right and left coronary arteries), both EST and MPI were negative (MPI or MPI and EST were positive in the other two patients). Perfusion imaging may be misleading in patients with diabetes because of small-vessel disease causing balanced ischemia (27), particularly because type 1 diabetic patients with autonomic neuropathy have difficulty increasing myocardial perfusion (28). Although MPI was performed after exercise in some patients and after dipyridamole in others, the proportion was similar between those with or without CAD. MPI after exercise and dipyridamole have similar sensitivity for predicting angiographic CAD (29), although the latter is a better predictor of cardiac events (30),

Although diabetic subjects with abnormal results of EST or MPI have increased cardiovascular risk, negative results of noninvasive tests are not entirely reassuring. Dobutamine stress echocardiography, adopted by many transplant programs (31), has modest sensitivity (52%) and is associated with an increased cardiac event rate (12). Nevertheless, 20% of subjects with negative dobutamine stress echocardiography results followed for 22 months reached a cardiac end point (12). In fact, a study in kidney-pancreas transplant candidates found that most cardiac events occurred in individuals with negative results of noninvasive tests (32). Therefore, intensive medical therapy was recommended for all subjects with any angiographic evidence of CAD.

Logistic equations based on clinical variables, often including the presence of diabetes itself, are superior to stress testing alone, whereas the addition of stress

testing to these models enhanced their performance (11). This is similar to our findings, although noninvasive testing did not enhance the performance of our model. Furthermore, it seems possible to identify a subgroup, albeit relatively small, at low risk for CAD using a simple clinical algorithm (13).

Could these data be explained by a selection bias causing subjects with silent CAD to be overrepresented? This seems unlikely because individuals with CAD were not excluded from assessment, although we cannot rule out a referral bias. Furthermore, subjects with significant renal impairment at high risk for silent ischemia were not eligible for assessment. Indeed, the long duration of diabetes in ITX candidates could suggest that they are survivors who might be expected to have a lower rate of CAD.

The management of asymptomatic coronary stenoses in type 1 diabetes is unclear. One study randomly assigned uremic diabetic subjects with CAD on angiography to revascularization or medical therapy (9). Those assigned to intervention had fewer cardiac events and fewer cardiac deaths, suggesting that asymptomatic CAD is not a benign condition.

Careful cardiac assessment before ITX is recommended. It is important to select individuals at low risk for premature coronary mortality because they could enjoy long-term benefits of ITX but also because the long-term impact of ITX and immunosuppression on CAD is unknown and finite procedural risks exist. Even most asymptomatic subjects will require angiography to reliably exclude the presence of CAD. Low-risk subjects with negative noninvasive tests may not require angiography. Noninvasive testing can guide decisions regarding the need for revascularization in subjects with CAD on angiography.

More generally, this study indicates the high risk of asymptomatic CAD in type 1 diabetic subjects with "difficult" diabetes, especially with advancing age and long duration of diabetes, although the roles of hypoglycemia unawareness and autonomic neuropathy warrant further examination. This study supports the hypothesis that asymptomatic CAD is highly prevalent in long-standing type 1 diabetic subjects with preserved renal function and supports aggressive risk factor management in these individuals. Routine angiography cannot be recommended for all patients with long-duration type 1 diabetes, but a high clinical index of suspicion for CAD is required and investigation of atypical symptoms is justified.

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