Insulin Resistance–Related Factors, but not Glycemia, Predict Coronary Artery Disease in Type 1 Diabetes

10-year follow-up data from the Pittsburgh Epidemiology of Diabetes Complications study

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OBJECTIVE — To determine the independent risk factors for coronary artery disease (CAD) in type 1 diabetes by type of CAD at first presentation.

RESEARCH DESIGN AND METHODS — This is a historical prospective cohort study of 603 patients with type 1 diabetes diagnosed before 18 years of age between 1950 and 1980. The mean age and duration of diabetes at baseline were 28 (range 8–47) and 19 years (7–37), respectively, and patients were followed for 10 years. Patients with prevalent CAD were excluded from the study. Electrocardiogram (ECG) ischemia was defined by Minnesota Code (MC) 1.3, 4.1–3, 5.1–3, or 7.1; angina was determined by Pittsburgh Epidemiology of Diabetes Complications (EDC) study physician diagnosis; and hard CAD was determined by angiographic stenosis ≥50%, revascularization procedure, Q waves (MC 1.1–1.2), nonfatal myocardial infarction (MI), or CAD death.

RESULTS — A total of 108 incident CAD events occurred during the 10-year follow-up: 17 cases of ECG ischemia, 49 cases of angina, and 42 cases of hard CAD (5 CAD deaths, 25 nonfatal MI or major Q waves, and 12 revascularization or ≥50% stenosis). Blood pressure, lipid levels, inflammatory markers, renal disease, and peripheral vascular disease showed a positive gradient across the groups of no CAD, angina, and hard CAD ($P < 0.01$, trend analysis, all variables), although estimated glucose disposal rate (eGDR) and physical activity showed inverse associations ($P < 0.01$, trend analysis, both variables). In addition, depressive symptomatology predicted angina ($P = 0.016$), whereas HbA_1 showed no association with subsequent CAD.

CONCLUSIONS — These data suggest that although the standard CAD risk factors are still operative in type 1 diabetes, greater glycemia does not seem to predict future CAD events. In addition, depressive symptomatology predicts angina and insulin resistance (eGDR) predicts hard CAD end points.

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Abbreviations: ABD, ankle-brachial difference; ABI, ankle-brachial index; AER, albumin excretion rate; ApoA1, apolipoprotein A1; BDI, Beck Depression Inventory; CAD, coronary artery disease; DCCT, Diabetes Control and Complications Trial; DSP, distal symmetric polyneuropathy; ECG, electrocardiogram; EDC, Epidemiology of Diabetes Complications; eGDR, estimated glucose disposal rate; E/I, expiration/inspiration; LEAD, lower extremity arterial disease; MA, microalbuminuria; MC, Minnesota Code; ON, overt nephropathy; WBC, white blood cell count.

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

See accompanying editorial, p. 1629.

Both type 1 and type 2 diabetes increase the risk of coronary artery disease (CAD) (1). However, the reasons underlying this are largely unknown, although renal disease (2) and the standard CAD risk factors seem important (3). The role of glycemic control is controversial; two studies (3,4) suggest little relationship to CAD, although others report such an association (5).

Although it has been an accepted practice to consider all CAD manifestations together, because they are believed to be linked by the same underlying atherosclerosis, important differences have been noted in the Pittsburgh Epidemiology of Diabetes Complications (EDC) study of type 1 diabetes. This study suggested somewhat distinct pathophysiologic mechanisms; for example, depressive symptomatology was more related to morbidity than mortality (3).

To further address these issues, risk factors, including glycemic control, for angina, ischemic electrocardiogram (ECG), and hard CAD (myocardial infarction [MI], CAD death, or angiographically proven stenosis) were investigated in this prospective study of type 1 diabetes using, for the first time, the 10-year incidence data.

RESEARCH DESIGN AND METHODS

— Subjects were participants in the Pittsburgh EDC Study, a 10-year prospective study of risk factors for complications of type 1 diabetes, and were recruited from the Children's Hospital of Pittsburgh registry of type 1 diabetes, which is representative of the Allegheny County population (6). All subjects had been diagnosed with type 1 diabetes at Children's Hospital (or seen there within 1 year of diagnosis) before 17 years of age between 1950 and May 1980 and were placed on continuous insulin

therapy at diagnosis, except for the honeymoon phase.

A total of 658 subjects met eligibility criteria and participated in the baseline examination in 1986–1988. Subjects were eligible (7) if they were alive, lived within 100 miles of Pittsburgh, and completed an initial survey (which had a 95% response rate). Subjects were then seen every 2 years, for a 10-year follow-up period ending in 1996–1998. Subjects refusing clinic attendance completed a medical history questionnaire. Only three subjects provided no follow-up data. A total of 52 subjects had CAD at baseline. Therefore, for hard CAD events (vide infra), follow-up is available for 603 subjects. Recruitment and study methods have been previously described (3,7,8).

Clinical evaluation and procedures

Before attending the clinic, participants completed a questionnaire including demographic information, medical history, the Beck Depression Inventory (BDI) for those >18 years of age (9), and the Harvard Alumni Health Study physical activity questionnaire (10). An ever smoker was defined as 100+ lifetime cigarettes.

Standardized sitting blood pressures were measured (11), and hypertension was defined as blood pressure ≥140/90 mmHg or use of antihypertensive medication. Ankle-brachial index (ABI) was determined using a Doppler blood-flow detector with the subject in the supine position; ABI <0.8 was considered positive (12). An ankle-brachial difference (ABD) ≥75 mmHg for any of the four vessels was considered positive for peripheral arterial calcification (12). The QT interval was corrected for ECG heart rate (13).

Fasting blood samples were analyzed for HbA_1 (microcolumn cation-exchange; Isolab, Akron, OH) for the first 18 months. After that time, automated high-performance liquid chromatography (Diamat; Bio-Rad, Hercules, CA; correlation $r = 0.95$) was performed. Lipoproteins/lipids were measured enzymatically (8), LDL cholesterol was calculated (14), and apolipoprotein A1 (ApoA1) was determined by immunoelectrophoresis (15).

Estimated glucose disposal rate (eGDR), a measure of insulin sensitivity, was calculated using regression equation (involving HbA_1, waist-to-hip ratio, and hypertension) derived from hyperinsulinemic-euglycemic clamp studies (16).

Distal symmetric polyneuropathy (DSP) was determined according to the Diabetes Control and Complications Trial (DCCT) clinical examination protocol (7), and overt nephropathy (ON) was defined as albumin excretion rate >200 and microalbuminuria (MA) 20–200 μg/min using multiple timed urine samples and immunoelectrophoresis (7). For 89 subjects taking part in a substudy at baseline, and from the 2-year follow-up onward, the expiration/inspiration (E/I) heart rate ratio was calculated (17); E/I <1.10 defined cardiac autonomic neuropathy.

Baseline ECGs were coded using the Minnesota Code (MC) (18): Q waves were defined as MC 1.1–1.2, and ischemic ECG was defined as MC 1.3, 4.1–4.3, 5.1–5.3, or 7.1. Hard CAD was defined as history of MI, confirmed by ECG Q waves or hospital records, or fatal CAD (19), coronary revascularization, or coronary artery occlusion ≥50% by angiography. Angina was determined by the EDC physician at each EDC cycle visit. A total of 11 subjects in whom angina developed between biennial visits, and who subsequently underwent coronary catheterization studies, are included in the "angina" group. Incident CAD was examined according to the earliest event: *1*) angina; *2*) ischemic ECG; or *3*) hard CAD.

Statistical analysis

Group differences were evaluated using Student's *t* test and χ^2 test. Non–normally distributed variables (e.g., triglycerides, albumin excretion rate [AER]) were transformed by natural log; Mann-Whitney *U* test was used to compare continuous variables that could not be log normalized (as indicated). $P < 0.05$ was considered statistically significant and the entry criterion for Cox proportional hazards modeling; a significance of $P > 0.10$ was applied for exclusion from the model. Due to small numbers of ischemic ECG, no multivariate models are presented for this end point. Because of colinearity with duration of diabetes ($r = 0.86$), age was not used in multivariate analyses; eGDR was modeled as a categorical variable (i.e., lowest quintile versus the rest). For Cox regression of specific types of CAD, which a priori were considered potentially distinct entities, subjects with CAD but without the type of interest as their earliest event were excluded from the specific analysis. Alternate Cox models were performed to determine which of certain interrelated variables were the better predictors (e.g., for renal disease, ON and MA, log AER, and creatinine alone were all separately considered). A similar approach was taken for the lipid markers and to compare prediction using eGDR alone or its components. Models were compared using the log likelihood ratios and Akaike's Information Criterion was used to calculate the number of degrees of freedom; the model having the lowest such value was designated the final (best) model. Because two risk markers (BDI and E/I) were only available on subgroups (≥18 years of age and 2-year follow-up examination onward, respectively), analyses with both of these variables were limited to a smaller group ($n = 322$). Any independent predictors identified from this subgroup were made available for modeling, along with the best set of predictors derived from the more complete data set to further determine their potential independence. (E/I did not enter any final Cox models and was not considered further.) No formal correction was performed for multiple comparisons. Analysis was performed using SPSS for Windows software (SPSS, Chicago, IL) (20).

RESULTS — Incident CAD events occurred in 108 of the 603 subjects (18% of men, 17% of women) after excluding the 52 baseline prevalent cases. A total of 42 subjects experienced a hard event (5 CAD deaths, 21 nonfatal MIs, 4 silent Q-wave MIs, and 12 coronary catheter-proven stenoses ≥50%), 49 subjects first developed angina, and 17 subjects first presented with ischemic ECG changes.

At baseline (Table 1), many variables (e.g., duration, fibrinogen, white blood cell count [WBC], lipoproteins, creatinine, physical activity, log AER, systolic blood pressure, eGDR, smoking, hypertension, DSP, E/I ratio, nephropathy, ABI/ABD) showed a gradient of worsening risk from no CAD to angina to hard CAD (all trend tests $P < 0.01$, except creatinine $P = 0.07$). The most prominent exceptions to the general pattern were HbA_1 and BDI. Similar HbA_1 concentrations were found among the groups, with a nonsignificant tendency for lower values in those with angina. Subjects with incident angina had the highest baseline depressive symptom scores ($P < 0.01$ vs. no

Table 1—*Baseline risk factor levels for CAD in both sexes, by first event, EDC 10-year follow-up*

Variable	No CAD	Angina	ECG ischemia	Hard CAD	Total CAD
n	495	49	17	42	108
Sex (% men)	50.1	49.0	35.3	61.9	51.9
Age (years)	25.9 ± 7.3	33.4 ± 6.2‡	32.0 ± 9.1†	32.9 ± 6.6‡	33.0 ± 6.8‡
Duration (years)	17.6 ± 6.9	25.1 ± 6.5‡	23.4 ± 8.8†	25.4 ± 6.4‡	24.9 ± 6.9‡
HbA_1 (%)	10.4 ± 1.8	9.9 ± 1.9	10.6 ± 1.4	10.7 ± 1.8	10.3 ± 1.8
Insulin dose/kg BW	0.81 ± 0.25	0.71 ± 0.18†	0.76 ± 0.22	0.75 ± 0.31	
Fibrinogen (mg/dl)§	280.1 ± 87.1	305.8 ± 77.9†	302.1 ± 94.6	343.3 ± 97.2‡	319.6 ± 89.5‡
WBC × 10^3/mm^2¶	6.4 ± 1.8	7.1 ± 2.2*	7.2 ± 2.4	8.1 ± 2.4‡	7.5 ± 2.3‡
Triglycerides (mg/dl)§	99.8 ± 82.7	113.4 ± 67.6*	145.8 ± 146.4	156.5 ± 80.1‡	134.4 ± 90.9‡
Non-HDL cholesterol (mg/dl)¶	130.7 ± 38.3	151.0 ± 42.0‡	145.4 ± 59.7	174.7 ± 48.5‡	159.2 ± 48.8‡
LDL cholesterol (mg/dl)¶	111.0 ± 30.8	125.3 ± 32.3†	119.9 ± 53.0	147.0 ± 44.0‡	132.4 ± 41.8‡
HDL cholesterol (mg/dl)	54.8 ± 12.2	50.9 ± 13.0*	51.3 ± 12.5	48.3 ± 9.8†	50.0 ± 11.8‡
ApoA1/HDL cholesterol	2.6 ± 0.5	2.8 ± 0.6*	2.9 ± 0.6*	2.9 ± 0.5‡	2.9 ± 0.5‡
Serum creatinine (mg/dl)§	0.96 ± 0.9	1.03 ± 0.5*	1.1 ± 1.3	1.6 ± 1.6‡	1.3 ± 1.2†
Log median AER (μg/min)§	3.2 ± 1.8	4.2 ± 2.1†	3.8 ± 2.3	5.9 ± 2.2‡	4.8 ± 2.3‡
Systolic blood pressure (mmHg)	111.1 ± 13.2	118.5 ± 14.1‡	113.8 ± 18.7	127.5 ± 21.1‡	121.3 ± 18.5‡
Corrected QT interval	407.1 ± 30.0	414.1 ± 25.9	418.0 ± 20.8	412.5 ± 29.6	414.1 ± 26.5*
Physical activity (kcal/week)§	2,790.9 ± 2,999.8	1,779.2 ± 2,176.4†	2,288.6 ± 2,412.7	1,917.4 ± 1,766.7	1,916.9 ± 2,053.6†
Waist-to-hip ratio	0.82 ± 0.07	0.84 ± 0.08*	0.82 ± 0.08	0.86 ± 0.07‡	0.85 ± 0.07‡
eGDR ($mg \cdot kg^{-1} \cdot min^{-1}$)§	8.1 ± 1.8	7.3 ± 2.0†	7.8 ± 1.9	6.4 ± 1.9‡	7.0 ± 2.0‡
BDI§	6.8 ± 6.2	9.7 ± 7.1†	3.9 ± 4.6	7.7 ± 5.7	8.1 ± 6.5*
Smoke ever (%)	32.8	50.0*	56.3	59.5†	54.7‡
Hypertension (%)	9.9	34.7‡	11.8‖	42.9‡	34.3‡
DSP (%)	20.3	61.2‡	35.3‖	50.0‡	52.8‡
E/I <1.10 (%)	12.9	32.6†	33.3*‖	47.1‡	37.9‡
ON (%)	17.2	38.8†	23.5‖	69.0‡	48.1‡
MA or ON (%)	38.8	69.4‡	41.2	85.7‡	71.3‡
ABI <0.8 or ABD 75+ (%)	6.4	14.3	17.63	26.8‡‖	19.6‡
eGDR <6.22 ($mg \cdot kg^{-1} \cdot min^{-1}$) (%)	14.1	22.4	18.8	56.1‡	34.9‡

Data are means ± SD or prevalence (%). Comparisons with no CAD: *$P < 0.05$; †$P < 0.01$; ‡$P < 0.001$. §Mann-Whitney *U* test; ‖Fisher's exact test; ¶log transformed before student's *t* test.

CAD). This difference was still apparent, although no longer significant, after excluding 22 cases occurring within 3 years of baseline (8.0 vs. 6.8). At baseline, there was no overall or sex-specific correlation between BDI and HbA_1. Subjects with ischemic ECG generally showed similar values to those with angina, except for higher triglycerides and physical activity and lower BDI score and hypertension prevalences. Of the putative cardiovascular risk factors in Table 1, only sex and HbA_1 did not predict total CAD. HbA_1 (upper limit normal 7.3%) ranged from 6.2 to 18.1%; the median value was 10.1%.

Risk factor levels were examined by sex when several sex differences were noted. Hard CAD was the earliest CAD in 46% of men and 31% of women ($P = 0.14$). BDI scores were generally higher in women than in men (8.6 vs. 6.1; $P < 0.001$) but predicted angina in both sexes. However, a low BDI score was seen in women who developed ischemic ECG (3.8 vs. 8.0; $P < 0.05$). Physical activity levels were higher in men than women, although sex patterns were similar with regard to CAD types. Corrected QT interval weakly predicted total CAD and angina only in men. Overall, there was little difference between HbA_1 levels in men (10.4%) and women (10.3%); however, lower HbA_1 levels in subjects in whom angina developed seemed more marked, although nonsignificantly, in men. Average eGDR was lower in men than women (7.1 vs. 8.5, $P < 0.001$) and in both sexes for those with incident total or hard CAD. Low ABI was more common in women, and high ABD was more common in men. The presence of either low ABI or high ABD predicted total CAD in each sex and hard CAD in men.

All significant ($P < 0.05$) univariate predictors were considered and examined using the strategy described in RESEARCH DESIGN AND METHODS for Cox modeling; the final best models are shown in Table 2. Duration of diabetes predicted total CAD overall and within each sex. The other independent predictors of total CAD were hypertension, WBC, HDL cholesterol, non-HDL cholesterol, and smoking history. In the subset with full data (see RESEARCH DESIGN AND METHODS), ApoA1/HDL cholesterol, ON, and corrected QT interval were independent predictors but did not enter the final model if made available, neither did BDI or eGDR. For hard CAD duration, ON, non-HDL cholesterol, WBC, and eGDR were independent predictors. Models without eGDR allowed hypertension and HDL to enter but provided a less optimal fit. For angina, hypertension, depressive symptomatology, and smoking were independent predictors. No significant sex interactions were found.

Table 2—*Independent baseline CAD predictors, both sexes, by type of first CAD event, Cox proportional hazards model*

Type CAD	Variables	HR (95% CI)	*P*	Other variables made available for modeling
Total CAD	Duration	2.18 (1.74–2.73)	<0.001	Apo A1/HDL ratio
	Hypertension	2.16 (1.40–3.32)	<0.001	Corrected QT interval
	WBC	1.35 (1.11–1.59)	0.002	ON
	HDL cholesterol	0.72 (0.58–0.91)	0.005	BDI
	Non-HDL cholesterol	1.33 (1.08–1.59)	0.007	
	Ever smoke	1.58 (1.05–2.38)	0.028	
n = 568, −2LL = 1,101.5				
Hard CAD	Duration	2.55 (1.74–3.75)	<0.001	BDI, and in model without eGDR
	ON	2.78 (1.29–6.02)	0.009	Hypertension
	Non-HDL cholesterol	1.36 (1.02–1.82)	0.036	
	WBC	1.52 (1.14–2.01)	0.004	
	eGDR	2.7 (1.3–5.6)	0.007	
n = 519, −2LL = 372.6				
Angina	Duration	2.36 (1.64–3.38)	<0.001	HbA_1
	Hypertension	3.06 (1.63–5.75)	<0.001	DSP
	Ever smoke	2.15 (1.18–3.90)	0.012	
	BDI	1.40 (1.06–1.84)	0.016	
n = 387, −2LL = 458.4				

Data are hazard ratios (95% CI). Hazard ratio (HR) yes/no or change per SD; SD WBC = 1.92×10^3, duration = 7.5 years, eGDR = 1.93 $mg \cdot kg^{-1} \cdot min^{-1}$, creatinine = 1.0 mg/dl, BDI = 6.48, HbA_1 = 1.84 mg%, ApoA1/HDL = 0.52, non-HDL cholesterol = 43.0 mg/dl, HDL cholesterol = 12.4 mg/dl.

CONCLUSIONS — Men and women with type 1 diabetes have a similarly increased risk of premature CAD, although, as shown, risk factors (predictors) vary by both sex and type of CAD manifestation. Of particular note is the lack of any positive association between HbA_1 and CAD in either sex and a weak, inverse association with angina. Depressive symptomatology (BDI) was an independent predictor of angina.

Notwithstanding these differing relationships between HbA_1, BDI, and CAD, the established CAD risk factors showed gradient worsening of baseline risk factors in subjects who did not develop CAD through incident angina (or ECG ischemia) to hard CAD, suggesting that angina and ECG ischemia are, at least to a degree, manifestations of the same underlying atherosclerotic process. The final model (Table 2) for total CAD underscores the multifactorial nature of CAD pathogenesis with independent prediction coming from time (duration), blood pressure (hypertension), inflammation/infection (WBC), lipids (HDL and non-HDL cholesterol), and smoking.

Another issue these data raise is whether non–Q-wave ischemia should be considered evidence of CAD or a risk factor/marker for clinical events. In a recent conference on the primary prevention of CAD, the presence of ST-segment changes on resting ECG was classified as a CAD risk factor (21). Perhaps the strongest evidence that ischemic ECG should be considered a CAD end point in type 1 diabetes is our recent demonstration that non–Q-wave ischemia predicts total mortality as well as established CAD does (22). Consistent with this is the demonstration that non–Q-wave ECG ischemia was predicted by ApoA1/HDL cholesterol and showed similar HDL cholesterol and triglyceride relationships as were seen for hard CAD. Strikingly however, BDI was very low in this group, a finding which may be spurious but is worthy of further follow-up.

The BDI measure of symptoms related to depression was first associated with CAD in this population in women by Lloyd et al. (23) at 4-year follow-up and later confirmed at 6 years in both sexes by Forrest et al. (3), whereas the current study shows that BDI is predominantly related to angina. This association is consistent with a recent review by Hemingway and Marmot (24) and the Normative Aging Study (25), which found that depression was more strongly associated with angina than total CAD using one (but not all) of their scales.

Of potential concern is the possibility that we have misdiagnosed noncardiac chest pain as angina. The diagnosis was, however, made by a research physician after careful exclusion, by history, of noncardiac causes and 40% of these subjects have already gone on to other manifestations of CAD, including MI in five (one fatality). The prediction of angina by greater smoking and depressive symptoms (and possibly lower HbA_1) raises the possibility that a certain subset may have a susceptible (anxious) personality state that might lead to coronary artery spasm in association with smoking and increased concern about blood glucose control.

The lack of any major predictive power of HbA_1 for CAD is both concerning and intriguing. This has been a consistent feature of our data throughout follow-up (3,23), even when using a measure of cumulative glycemic exposure (3).

Furthermore, a cross-sectional comparison with the large EURODIAB type 1 diabetes study of complications (26) showed, in the comparable EURODIAB subgroup, an inverse association of HbA_{1c} and CAD in women. The DCCT/EDC study has so far had insufficient events to examine this issue. Interestingly, earlier EDC analyses (3) and reports from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (27) have shown HbA_1 to be a strong independent predictor of lower extremity arterial disease (LEAD). We postulate that this paradox is related to the different methods of presentation of CAD and LEAD, i.e., chronic arterial obstruction in LEAD (detected by low ABI amputation or claudication) but plaque rupture in CAD (detected by MI, CAD death). Therefore, in type 1 diabetes (and probably type 2 diabetes as well), we hypothesize that although hyperglycemia may be related to the more extensive atherosclerosis seen on a proportionate basis, fewer of the plaques so formed are vulnerable and likely to rupture and cause acute coronary events. This would explain the stronger relationship between HbA_1 and LEAD than with CAD, and the relatively weak overall glycemia-CAD relationship (28). It should be noted that in older type 1 diabetic subjects, a direct glycemia CAD relationship has been noted in one study raising the possibility of an age-glycemia interaction (5).

This concept of more extensive but less vulnerable atherosclerosis in type 1 diabetes is consistent with the general nature of type 1 diabetes complications, which involve increased tissue stiffness and sclerosis (e.g., glomerulorsclerosis, fibrous proliferative retinopathy, limited joint mobility) and are, at least partially, mediated by increased advanced glycosylation end product formation and protein cross-linking (29) and cellular proliferation from increased growth factors (30). Other consistent features are the greater tendencies in diabetes to concentric rather than eccentric plaques, negative remodeling of the arterial wall (31), and in morphological studies increased fibrous tissue and decreased foam cell/macrophage and lipid content (32). From a clinical viewpoint, a smaller proportion of sudden deaths or unstable angina presentations are attributed to plaque rupture (33).

Previous reports from the Pittsburgh EDC Study and the DCCT have raised the possibility that insulin resistance, the hallmark of type 2 diabetes, may also relate to CAD risk in type 1 diabetes (34,35). Using an equation (16) for eGDR as a marker for insulin resistance, the current data show eGDR to be univariately predictive of hard and total CAD overall and in both sexes and, multivariately, of hard CAD overall. Although it could be argued that our eGDR is only a statistical computation using other risk factors, it is nonetheless clear that the prediction so afforded is closely related to insulin resistance (16). Interestingly, all factors herein predicting total CAD, hard CAD, or angina have been linked to insulin resistance.

WBC, potentially a marker for both the inflammatory and infective components of atherosclerosis, may also have an etiologic role by participating in endothelial injury and clogging capillaries and, interestingly, displaces triglycerides from the Cox model for total CAD, raising the possibility that triglycerides may predict CAD more as a function of inflammation than lipoprotein atherogeneity.

The current study also confirms the importance of renal disease, especially in men (3), hypertension, smoking, and dyslipidemia as CAD predictors in type 1 diabetes (Table 2). Interestingly, the entire lipid profile (HDL and non-HDL cholesterol) was independently predictive, the latter measure being marginally better than LDL cholesterol and triglycerides.

In conclusion, in subjects with type 1 diabetes, most established cardiovascular risk factors strongly predicted total CAD (and its major subtypes) in 10-year follow-up. However, HbA_1 did not predict hard CAD and showed a weak inverse association with angina, which was also predicted by depressive symptomatology. These observations have major significance in terms of prevention and treatment and suggest that, in terms of CAD, we may do better to address traditional risk factors, including insulin resistance, inflammatory markers, and depressive symptomatology, rather than focus on glycemic control, which, nonetheless, merits close control for the prevention of microvascular complications.

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