Glycemia (or, in Women, Estimated Glucose Disposal Rate) Predict Lower Extremity Arterial Disease Events in Type 1 Diabetes

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The purpose of this study was to determine the predictors of lower extremity arterial disease (LEAD) events in a type 1 diabetes population. Data are from the Pittsburgh Epidemiology of Diabetes Complications Study of childhood onset type 1 diabetes. At baseline, the study population had a mean age 28 (range, 8 to 47) years and duration 19 (range, 7 to 37) years. LEAD events, assessed by questionnaire or clinical examination, were defined as claudication (Rose questionnaire), foot ulceration, or lower extremity amputation. Estimated glucose disposal rate (eGDR), a measure of insulin resistance, was calculated from glycosylated hemoglobin (HbA_1), waist-to-hip ratio (WHR), and hypertension using an equation previously validated with hyperinsulinemic euglycemic clamp studies. There were incident LEAD events in 70 of 586 subjects during 10 years follow-up, giving an incidence density of 1.3 events/100 person-years. Incidence did not differ by gender. Major predictors of LEAD events were diabetes duration, low-density lipoprotein-cholesterol (LDL-C), heart rate, eGDR, log albumin excretion rate (AER), systolic blood pressure (SBP), hypertension, proliferative retinopathy, distal symmetric polyneuropathy, and overt nephropathy (each $P < .001$). HbA_1, low ankle brachial index (ABI) (<0.9), and a high ankle brachial difference (ABD) (SBP ≥ 75 mm Hg) also predicted LEAD events. Cox modeling suggested that duration ($P < .001$), HbA_1 ($P < .001$), hypertension ($P = .006$), log albumin excretion rate ($P = .011$), and heart rate ($P = .028$) predicted events independently. The overall model with HbA_1 and hypertension was significantly better than with eGDR, while the alternate models in men were similar. In women, the model with eGDR showed a significantly better fit. Glycemia, insulin resistance, hypertension and renal disease are powerful predictors of symptomatic lower extremity arterial disease in type 1 diabetes.

DIABETES MELLITUS IS associated with increased risk for lower extremity claudication, ulceration, and amputation,[1] conditions leading to prolonged disability or hospitalization, coronary artery disease (CAD), stroke, and early mortality.[2,3] Although cross-sectional associations between cardiovascular risk factors and lower extremity arterial disease (LEAD) have been reported,[1] there have been few prospective studies in type 1 diabetes (T1D). Given the younger age of onset of T1D compared with the more common type 2, it is likely that differences in LEAD incidence and risk factors exist between the 2 major types of diabetes. Furthermore, little is known as to whether the recent suggestions that markers of insulin resistance, eg, waist-to-hip ratio (WHR,[4] a family history of type 2 diabetes (T2D),[5] and excessive weight gain on intensive insulin therapy[6] may increase coronary disease risk, applies to atherosclerosis of the lower extremities and its sequelae.

The Pittsburgh Epidemiology of Diabetes (EDC) Study has recently developed an equation to estimate glucose disposal rate (eGDR), derived from hyperinsulinemic euglycemic clamp studies[7] and have reported that it predicts CAD incidence and all-cause mortality.[8,9] We have also recently reported that measures of subclinical atherosclerosis, including the ankle brachial index (ABI), a measure of LEAD, also predict these endpoints in T1D.[9,10] To determine how these factors relate to clinical LEAD events (claudication, ulceration, and amputation), they were examined in the context of the extensive range of established cardiovascular risk factors assessed in the EDC study at baseline.

MATERIALS AND METHODS

Study Population

Subjects were participants in the Pittsburgh EDC Study, a 10-year prospective study of risk factors for complications of T1D. EDC participants were recruited from the Children's Hospital of Pittsburgh registry of T1D, which is representative of the Allegheny County population.[11] Subjects diagnosed before age 17 years and between 1950 and May 1980 with T1D at Children's Hospital (or seen there within a year of diagnosis) were eligible for the EDC study. Recruitment and study methods have been previously described.[12-14]

A total of 658 subjects met eligibility criteria and participated in the baseline examination in 1986 to 1988. Subjects were then seen every 2 years for 10 years follow-up ending in 1996 to 1998. Those refusing clinic attendance completed a medical history questionnaire. Through the EDC examination cycle in 1996 to 1998 (10-year follow-up), follow-up data for LEAD events were available on all but 26 subjects.

Clinical Evaluation and Procedures

Before attending the clinic, participants completed a questionnaire including demographic information, medical history, the Beck Depression Inventory (BDI) for those aged 18+ years,[15] and physical activity (Harvard Alumni Health Study questionnaire).[16] An ever smoker was defined as 100+ lifetime cigarettes.

Sitting blood pressures were measured according to the Hypertension Detection and Follow-up Program protocol,[17] hypertension being defined as blood pressure ≥ 140/90 mm Hg or taking antihypertensive medication. ABI was determined using a Doppler blood-flow detector with the subject supine. The right and left tibialis posterior and dorsalis pedis systolic pressures were compared with the arm pressure, an ABI

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in any vessel less than 0.9 being categorized as low. An ankle brachial difference (ABD) of ≥ 75 mm Hg for any of the 4 vessels was considered positive for peripheral arterial calcification.[18]

The QT interval was derived from a single waveform in electrocardiograph (ECG) lead II and was corrected for ECG heart rate according to Bazett's formula.[19] Ventricular heart rate was determined by ECG, however, if the baseline ECG was missing for a patient, the pulse measured by the EDC nurse was used (n = 21).

Fasting blood samples were analyzed for hemoglobin A_1 (HbA_1), lipid, inflammatory, and other risk markers. HbA_1 was measured in saline-incubated samples by microcolumn cation-exchange (Isolab, Akron, OH for the first 18 months after which automated high-performance liquid chromatography (Diamat, Bio-Rad, Hercules, CA) was used, which yielded almost identical results (r = .95). Cholesterol and triglycerides were measured enzymatically,[20,21] as was high-density lipoprotein-cholesterol (HDL-C) after a heparin and manganese procedure.[22] Low-density lipoprotein-cholesterol (LDL-C) was calculated using the Friedewald[23] equation previously validated in this population.[24] Apolipoprotein A-1 was determined by immunoelectrophoresis.[25]

Fibrinogen was determined with a biuret colormetric procedure and a clotting method, and white blood cell (WBC) counts using the Coulter (Hialeah, FL) S-Plus IV. eGDR, an inverse marker of insulin resistance, was calculated using a previously described formula derived from hyperinsulinemic euglycemic clamp studies.[7] The eGDR formula was developed through study of 24 subjects who were chosen so as to have equal numbers at low, medium, and high risk of insulin resistance, based on age-specific clinical factors. Using linear regression, the best combination of risk factors (hypertension, WHR, and HbA1) for the prediction of measured glucose disposal was derived and expressed by the equation eGDR=24.31-12.22(WHR)-3.29(HTN)-0.57(HbA_1).

As previously described,[13] distal symmetric polyneuropathy (DSP) was determined according to the Diabetes Control and Complications Trial clinical examination protocol[26] and nephropathy (overt: albumin excretion rate [AER] >200, microalbuminuria: 20 to 200 μg/min) using multiple timed urines.[27]

For 89 subjects taking part in a substudy at baseline and from Cycle 2 onwards, the expiration/inspiration (E/I) heart rate ratio was calculated using an office-based method from ECG.[28] An E/I ratio less than 1.10 was considered evidence of autonomic neuropathy. Baseline E/I ratio was imputed for those without it using the next available measure if it was greater than 1.10 and if the subjects did not have CAD at the cycle E/I was first available, otherwise the baseline variable was treated as missing.

The baseline ECGs were coded using the Minnesota Code (MC),[29] Q-waves were defined as MC 1.1 to 1.2, and ischemic ECG as MC 1.3, 4.1 to 4.3, 5.1 to 5.3, or 7.1. Hard CAD was defined using standard criteria as a history of MI confirmed by ECG Q-waves or hospital records,[30] fatal CAD,[31] coronary revascularization or coronary artery occlusion ≥ 50% by angiography. Angina was determined by the EDC physician at each EDC cycle visit. Eleven subjects, who developed angina between biennial visits and 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. If major Q-waves occurred concurrently with ST-T changes, the patient was classified preferentially into hard CAD. Fifty-two subjects with prevalent CAD at baseline were excluded.

Claudication was determined by the Rose questionnaire.[32] Lower extremity ulceration and amputation were determined by patient self-report of hospitalization for these causes and by the EDC clinical physician using an ulcer grading protocol: normal, ischemic, venous stasis, neurotropic, or type uncertain. For this analysis, we have excluded ulcers classified as venous stasis or neurotropic. Thus, the definition of lower extremity clinical events (LEAD event) is any of claudication, "ischemic" or "type uncertain" ulceration, gangrene, amputation, infection, or necrobiosis diabeticorum.

Forty-six subjects (21 men, 25 women) with prevalent LEAD events at baseline were excluded. Fourteen subjects had an ulcer, and 11 had an amputation noted by the examining physician at baseline, while 19 had claudication. Two additional subjects were considered to have baseline LEAD events, as they reported in later EDC cycles having had an ulceration prior to the first examination date (presumably the ulcer had healed).

Statistical Analysis

Differences between subjects were evaluated using Student's t test for continuous variables and χ^2 test for dichotomous variables. Non-normally distributed variables were transformed by natural log; the Mann-Whitney test was used to compare continuous variables that could not be log-normalized. P less than .05 was considered statistically significant.

Variables that were correlated at the $P < .05$ level with the LEAD end point were made available for Cox proportional hazards modeling. Significance of $P < .05$ was required to enter the model and $P > .10$ for exclusion from the model of a variable, which had entered.

Because of colinearity with diabetes duration (r = .86), the age variable was not used in multivariate analyses. Estimated GDR was modeled as a continuous variable. A variable indicating either ABI abnormal (<0.9) or ABD abnormal (75+ mm Hg) was stronger than either component separately and was used in multivariate models. Analysis was performed using SPSS for Windows (SSPS, Chicago, IL.[33]

RESULTS

There were incident LEAD events in 70 of the 586 subjects (11% of men, 13% of women). A total of 40 first events were claudication, 13 amputation, 10 ulcer, and 7 combined, with no gender differences in type of first event.

Table 1 shows the LEAD event predictors for both sexes. A large number of cardiovascular risk factors predicted LEAD events, including age and duration, lipoproteins (LDL-C or non–HDL-C, but not HDL-C or triglycerides), fibrinogen, WBC, blood pressure, AER, heart rate, QT interval corrected for heart rate (QTc), microvascular complications, smoking, and greater depressive symtomatology (BDI). Estimated GDR strongly predicted LEAD events as, to a degree, did each of its components: HbA_1, WHR, and hypertension. Associations of ABI less than 0.9 and ABD 75+ with LEAD events failed to reach significance, but a marker for the presence of either abnormality predicted LEAD events. Ischemic ECG and CAD did not predict LEAD events. When examined separately by gender (Table 2), few differences were noted, although a low ABI was both more prevalent and more predictive among women ($P < .01$), a feature not seen in men. High ABD was more prevalent among men, but not predictive in either gender. The mean eGDR was lower among men than women. Glycosylated hemoglobin and BDI score were more strongly predictive of LEAD events in men ($P < .01$, $P < .05$, respectively) than women (nonsignificant).

Table 3 shows the independent LEAD event predictors overall. Diabetes duration ($P < .001$), glycosylated hemoglobin ($P < .001$), hypertension ($P = .006$), log AER ($P = .011$), and heart rate ($P = .028$) independently predicted LEAD events. This model was significantly better than one with eGDR instead of HbA_1 and hypertension.

Table 1. Baseline Risk Factor Levels for Incident LEAD Events, 10-Year Follow-up

Variable	No.	No LEAD	LEAD Events
Total population	586	516	70
Male (%)	586	51.9	47.1
Age (yr)	586	26.5 ± 7.6	31.3 ± 7.1*
Duration (yr)	586	18.1 ± 7.2	23.4 ± 7.1*†
HbA_1 (%)	583	10.3 ± 1.8	10.9 ± 1.9‡§
Fibrinogen (mg/dL)	578	282.3 ± 89.4	312.3 ± 88.7†§
WBC × $10^3/mm^2$	580	6.4 ± 1.8	7.0 ± 2.3‖§
Triglycerides (mg/dL)	552	104.3 ± 85.8	114.0 ± 69.5†
Non-HDL-C (mg/dL)	580	131.6 ± 39.3	154.4 ± 43.3*§
LDL-C (mg/dL)	540	111.7 ± 32.9	130.7 ± 35.7*§
HDL-C (mg/dL)	580	53.9 ± 12.0	55.2 ± 13.9
ApoA1/HDL-C	572	2.6 ± 0.5	2.7 ± 0.6
Estimated GDR	578	8.0 ± 1.8	6.5 ± 2.1*†
Serum creatinine (mg/dL)	582	1.0 ± 0.8	1.3 ± 1.6†
Log median AER (μg/min)	582	3.3 ± 1.9	4.8 ± 2.1*†
SBP (mm Hg)	586	112.1 ± 14.7	120.5 ± 18.6*†
DBP (mm Hg)	586	72.1 ± 10.7	76.7 ± 11.9‡
Heart rate	585	74.4 ± 12.7	81.6 ± 13.0*
QTc (Bazett)	557	407.4 ± 30.1	416.4 ± 28.8‖
WHR	581	0.82 ± 0.07	0.84 ± 0.08‖
BDI	471	6.8 ± 6.1	8.4 ± 6.1‖†
E/I ratio	512	1.29 ± 0.19	1.18 ± 0.17*†
E/I ratio < 1.10 (%)	512	14.5	40.4*
Smoke ever (%)	560	34.1	48.6‖
Hypertension (%)	586	12.2	38.6*
Proliferative retinopathy (%)	576	24.3	52.9*
Neuropathy (%)	584	22.6	47.1*
Nephropathy (%)	586	19.8	44.3*
ABI < 0.9 (%)	580	6.7	12.9
ABD 75+ (%)	580	4.9	10.0¶
ABI < 0.9 or ABD 75+	580	11.4	22.9‖
Ischemic ECG (%)	575	4.5	1.5¶
CAD (%)	586	3.1	4.3¶

NOTE. Values are given as mean ± SD or prevalence (%).

Abbreviations: ABD, ankle brachial difference; ABI, ankle brachial index; AER, albumin excretion rate; BDI, Beck Depression Inventory; CAD, coronary artery disease; DBP, diastolic blood pressure; ECG, electrocardiograph; eGDR, estimated glucose disposal rate; HbA_1, hemoglobin A_1; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; SBP, systolic blood pressure; WBC, white blood cells; WHR, waist-to-hip ratio; ApoA1, Apoprotein A1; E/I ratio, expiration/inspiration ratio.

Comparisons by LEAD status: *$P < .001$, ‡$P < .01$, ‖$P < .05$.

†Mann-Whitney, ¶Fisher's exact.

§Log-transformed before *t* test.

Tables 4 and 5 show the independent predictors of LEAD events for men and women, respectively. Among men, duration, HbA_1 ($P < .001$) and log AER entered the prediction model; however a model with duration, eGDR ($P = .005$) and log AER gave a similar prediction and fit.

Among womem, duration, eGDR, and the presence of either abnormal low or high ankle pressures predicted LEAD events. The model with eGDR ($P < .001$) was significantly better than models with duration, abnormal ABI/ABD, and any third variable of glycosylated hemoglobin ($P = .10$), WHR ($P = .03$), hypertension ($P < .001$), or SBP ($P = .019$).

DISCUSSION

This report focuses on clinical LEAD events, namely claudication, ulceration, and amputation. As such, the pathogenesis probably involves neuropathic components, as well as atherosclerotic arterial disease. Indeed, ABI was only a weak predictor of these outcomes overall and in men.

Glycosylated hemoglobin, which is a component of the eGDR, independently predicted LEAD events in men, and there was no significant difference between using eGDR or HbA^1 in men. However, HbA_1, together with hypertension (also part of the eGDR), resulted in a significantly better model for both genders combined, while eGDR resulted in a significantly better prediction model in women. It would thus appear that insulin resistance and/or glycemia are major determinants of LEAD events, consistent with the concept that microvascular and neurologic involvement is also pertinent. Indeed, proliferative retinopathy, neuropathy (both DSP and autonomic neuropathy, eg, E/I ratio) and nephropathy were all predictive univariately.

Men and women with T1D have an increased risk of premature LEAD events and, as is the case for CAD, there is no significant gender difference.[12] While we found several risk factors, including eGDR, to be common predictors of both CAD and LEAD events,[12] HbA_1, as reported here, is a strong risk factor for LEAD events, but not CAD, while some lipid fractions (HDL-C, triglycerides) predicted CAD, but not LEAD events. The reasons underlying these contrasts are not clear, although we have previously postulated that the lack of a strong glycemic-CAD association despite a strong glycemia-LEAD link may reflect the potential effect of glycemia to selectively promote certain components of plaque formation (eg, smooth muscle cell and macrophage proliferation, fibrous tissue deposition, advanced AGE-mediated cross-linking). While this would tend to increase the extent of atherosclerosis, it may also lead to less vulnerable plaques. As CAD events result primarily from rupture of vulnerable plaques and LEAD events reflect chronic ischemia, the differing links with HbA_1 can be so explained. Previous studies in both T1D 1 and T2D have also reported that HbA_1 levels predict the development of LEAD, whether the endpoint is determined by ABI, amputation, or symptomatic claudication.[34,35]

Levin et al[36] has suggested that LEAD is both a macrovascular and microvascular disease, although this is controversial. The Diabetes Control and Complications Trial (DCCT) established that tight blood glucose control could reduce the incidence of microvascular complications in T1D.[37] It is also interesting to note that the suggestive evidence of benefit on macrovascular events in DCCT was largely based on LEAD (claudication) events rather than coronary events.[37] The association between blood glucose, foot ulceration, and limb loss is likely to reflect, at least partially, the intermediate complication of neuropathy,[38] leading to both foot deformity and loss of sensation, as well as the detrimental effect of high blood sugar on wound healing.[39]

We recently developed an equation for estimating glucose disposal rate as a marker for insulin resistance in T1D based on euglycemic hyperinsulinemic clamp studies,[7] such clamp studies being impractical for large populations. Whether the use of

Table 2. Baseline Risk Factor Levels for Incident LEAD Events, by Sex, EDC 10-Year Follow-up

Variable	Male		Female	
	No LEAD	LEAD	No LEAD	LEAD
No.	268	33	248	37
Age (yr)	26.1 ± 7.4	33.1 ± 6.9*	26.8 ± 7.8	29.6 ± 6.9†
Duration (yr)	18.1 ± 7.0	25.0 ± 6.5*	18.1 ± 7.3	22.0 ± 7.3‡
HbA_1 (%)	10.3 ± 1.8	11.4 ± 2.0‡§	10.3 ± 1.8	10.5 ± 1.8
Fibrinogen (mg/dL)	271.0 ± 90.5	300.6 ± 78.7†§	294.5 ± 86.7	322.8 ± 96.7§
WBC × $10^3/mm^2$	6.4 ± 1.8	6.6 ± 1.8§	6.5 ± 1.8	7.4 ± 2.7†§
Triglycerides (mg/dL)	113.7 ± 94.0	127.9 ± 73.9‖	94.3 ± 75.0	102.1 ± 64.6‖
Non-HDL-C (mg/dL)	134.6 ± 41.2	165.5 ± 46.0*§	128.4 ± 37.0	144.3 ± 38.5†
LDL-C (mg/dL)	113.8 ± 35.3	139.4 ± 35.9*§	109.5 ± 30.0	123.2 ± 34.3†
HDL-C (mg/dL)	49.5 ± 9.5	48.4 ± 10.6	58.7 ± 12.5	61.4 ± 13.7
ApoA1/HDL-C	2.8 ± 0.5	2.9 ± 0.6	2.5 ± 0.5	2.5 ± 0.5
Estimated GDR	7.4 ± 1.7	5.6 ± 2.0*§	8.7 ± 1.6	7.4 ± 1.9‡‖
Serum creatinine (mg/dL)	1.1 ± 0.9	1.6 ± 2.1‖	0.9 ± 0.7	1.0 ± 0.6‖
Log median AER (μg/min)	3.4 ± 2.0	5.4 ± 2.0*‖	3.1 ± 1.9	4.3 ± 2.0‡§
SBP (mm Hg)	115.4 ± 15.9	125.1 ± 16.7*‖	108.4 ± 12.1	116.4 ± 19.5†§
DBP (mm Hg)	74.4 ± 11.2	79.2 ± 9.3†	69.6 ± 9.6	74.5 ± 13.5†§
Heart rate	71.1 ± 12.0	78.0 ± 12.7‡	78.0 ± 12.6	84.8 ± 12.7‡
QTc	398.6 ± 28.7	407.5 ± 24.7	417.1 ± 28.7	423.4 ± 30.2
WHR	0.87 ± .05	0.90 ± .05‡§	0.77 ± .06	0.79 ± .06†
BDI	5.4 ± 5.2	8.0 ± 6.8†‖	8.2 ± 6.7	8.7 ± 5.5‖
Exp/Inspir	1.30 ± 0.19	1.18 ± 0.16‡‖	1.28 ± 0.18	1.19 ± 0.17†‖
E/I ratio (% < 1.10)	14.8	40.7‡	14.2	40.0‡
Smoke ever (%)	38.1	51.5	29.8	45.9
Hypertension (%)	14.9	39.4‡	9.3	37.8*¶
Proliferative retinopathy (%)	24.5	57.6*	24.1	48.6‡
Neuropathy (%)	24.0	57.6*	21.1	37.8†
Nephropathy (%)	22.0	51.5‡	17.3	37.8‡
ABI < 0.9 (%)	7.2	0.0¶	6.1	24.3‡¶
ABD 75+ (%)	8.0	15.2¶	1.6	5.4¶
ABI < 0.9 or ABD 75+	14.8	15.2¶	7.7	29.7*¶
Ischemic ECG (%)	4.9	3.4¶	4.1	0.0¶
CAD (%)	3.7	3.0¶	2.4	5.4¶

NOTE. Values are given as mean ± SD or prevalence (%).

Abbreviations: ABD, ankle brachial difference; ABI, ankle brachial index; AER, albumin excretion rate; BDI, Beck Depression Inventory; CAD, coronary artery disease; DBP, diastolic blood pressure; ECG, electrocardiograph; EDC, Epidemiology of Diabetes Complications; eGDR, estimated glucose disposal rate; HbA_1, hemoglobin A_1; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; SBP, systolic blood pressure; WBC, white blood cells; WHR, waist-to-hip ratio; ApoA1, Apoprotein A1; E/I ratio, expiration/inspiration ratio.

§Log-transformed before testing: †$P < .05$, ‡$P < .01$, *$P < .001$.

‖Mann-Whitney, ¶Fisher's exact.

this equation (based on WHR, hypertension, and HbA_1) reflects anything more than a statistical computation is difficult to discern, for its use in the multivariate models is only superior to its components in women. Nonetheless, the prediction provided by eGDR does represent GDR quite closely, ($r = .76$) and reduced GDR is thought by many to be a major underlying feature of glucose intolerance and hypertension and to result from excess visceral adiposity (represented by WHR). A pathophysiologic role for impaired glucose disposal would seem

Table 3. Cox Proportional Hazards Model for 10-Year Incident LEAD Events, Both Sexes

Variables	Hazard Ratio (95% CI)	*P*
Duration	1.74 (1.34, 2.27)	<.001
HbA_1	1.53 (1.22, 1.92)	<.001
Hypertension	2.23 (1.24, 4.02)	.008
Log AER	1.39 (1.07, 1.79)	.013
Heart rate	1.33 (1.03, 1.71)	.024
N = 574		

NOTE. Hazard ratio yes/no or change per SD (duration 7.5 yr; HbA_1 1.84%; log AER 2.01 μg/min; heart rate 12.95/min).

Table 4. Cox Proportional Hazards Model for 10-Year Clinical LEAD Incidence, Males

Variables	Hazard Ratio (95% CI)	*P*
HbA_1	1.70 (1.27, 2.29)	<.001
Duration	2.01 (1.37, 2.94)	<.001
Log AER	1.82 (1.30, 2.54)	<.001
N = 295		

NOTE. Hazard ratio yes/no or change per SD (duration 7.5; HbA_1 1.84; log AER 2.01).

Table 5. Cox Proportional Hazards Model for 10-Year Clinical LEAD Incidence, Females

Variables	Hazard Ratio (95% CI)	*P*
eGDR	0.45 (0.32, 0.64)	<.001
ABI < 0.9 or ABD 75+	3.13 (1.52, 6.44)	.002
Duration	1.48 (1.01, 2.07)	.022
N = 280		

NOTE. Hazard ratio yes/no or change per SD (duration 7.5; GDR 1.93; log AER 2.01).

likely and, thus, raises the possibility that other features of insulin resistance may be of relevance. In addition to CAD, all-cause mortality, and LEAD events, eGDR also predicts the development of overt nephropathy.[8] One possible hypothesis for a specific effect of insulin resistance is that it may allow vasoconstrictors to act unopposed, resulting in increased risk of claudication and other vascular entities.[40]

The failure of CAD at baseline to predict subsequent LEAD events is compatible with our earlier report, in which the incidence of ABI less than 0.9 or amputation was actually lower among patients with CAD than without.[12] Other studies have failed to link CAD with subsequent amputation[34] and have offered the explanation that CAD patients may not be considered good surgical candidates. In the present study, most subjects with prevalent CAD were excluded because of coexisting LEAD at baseline, so a weak association cannot be excluded.

Data are few in T1D concerning the risks posed by asymptomatic large vessel peripheral arterial disease detected by a low ratio of ankle: brachial blood pressure. A complicating element in the measurement of peripheral arterial pressure is that medial arterial wall calcification, which is common in T1D of long duration, may reduce compressibility of the artery by a cuff, leading to elevated pressure recordings.[18] In the present study, a low ABI predicted LEAD events among women and overall, while a high ABD was more prevalent among men. ABD $\geq$ 75 mm Hg is a marker for medial arterial wall calcification, which may have obscured vascular occlusion, especially in men. Although medial wall calcification does not occlude the artery, it does predict cardiovascular and total mortality.[9,41] A combined marker for abnormal ABI/ABD was a univariate LEAD event predictor overall and an independent LEAD event predictor in women. Therefore, we recommend that in screening for risk of LEAD events, as for CAD risk, both ABI and ABD be recorded as both a low ABI or high ABD to identify high-risk diabetic patients.

The QT interval represents ventricular repolarization and is controlled by the balance of sympathetic and parasympathetic stimuli. The QTc interval has been implicated in sudden cardiac death among patients with a history of myocardial infarction[42] and T2D[43]; however, its usefulness in T1D is disputed.[44]. We found a weak predictive effect for LEAD events. In our recent analyses, QTc did not predict total mortality.[9]

The univariate predictive power of WBC count, smoking, age, diabetes duration, fibrinogen, and depressive symptomatology for LEAD events are consistent with our 6-year follow-up report for LEAD, as determined by ABI less than 0.9 and amputation,[12] although it should be noted that the end points in these 2 reports are not the same. Nonetheless, others have reported that the cross-sectional correlates of symptomatic and asymptomatic peripheral vascular disease are similar[45] and include smoking[46] and renal disease.[47] Two further findings appear novel and intriguing.

First, the unusually strong association of heart rate to LEAD events, which would appear, at first pass, to be explained by its acting as a proxy for autonomic neuropathy, also a LEAD event predictor. Heart rate, rather than E/I ratio, a more direct measure of parasympathetic autonomic heart rate, however, entered the multivariate model overall. While this may reflect the smaller sample size available for the E/I ratio, it might also suggest that heart rate better predicts the true pathology, perhaps because it includes a sympathetic element as well.

The second surprising result was the lack of predictive power by HDL-C and/or triglycerides. We have previously reported[12] that LDL-C, but not HDL-C or triglycerides, predicted LEAD, determined by ABI less than 0.9 or amputation. The present analysis reached similar results (ie, either LDL-C or non–HDL-C) predicted symptomatic LEAD, but HDL-C or triglycerides do not, despite these fractions being strong CAD and mortality risk factors.[9,12] The Program on Surgical Control of Hyperlipidemias found that cholesterol modification significantly reduced the risk of a combined claudication or ABI less than 0.95 end point, with a relative risk of 0.7,[48] while a review of 9 trials[49] noted that LDL-C lowering produced marked, but nonsignificant, reduction in fatal events (odds ratio [OR], 0.21). Another report suggested that the association of lipids and lower extremity disease is surprisingly weak.[46] Traditionally, triglycerides have been thought of as a major risk factor for LEAD in the general population, and their absence as a predictor in our study is perplexing, especially given their prediction of both CAD and nephropathy.

In conclusion, diabetes duration, glycemia, heart rate, and renal status independently predicted LEAD events in T1D. Reduced EGDR (ie, insulin resistance) gave equally strong prediction in men, and in women, appeared a little more powerful than its components (HbA_1, hypertension, WHR), although the components were stronger in the overall model. While risk of an LEAD event did not differ by gender in this population and both genders shared many risk factors, nephropathy was relatively more important in men and low ankle pressure in women. The eGDR and the determination of ABI and difference, may be useful screening tools for lower extremity vascular complications in T1D, especially among women, while the glycemic level may be most useful among men. Given the prediction by eGDR, hygienic interventions, which enhance insulin sensitivity (eg, weight loss and exercise) may be particularly beneficial.

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