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Lower-extremity arterial calcification as a correlate of coronary artery calcification

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Abstract

Coronary artery calcification (CAC) has been used as a testing modality for coronary atherosclerosis burden. In diabetes, arterial calcification in the tunica media is common and predicts renal and cardiovascular mortality. It is unknown whether the 2 calcification processes are related. We identified risk factors associated with lower-extremity arterial calcification (LEAC) and determined its relationship to the presence of CAC 6 years later and the incidence of complications in type 1 diabetes mellitus. A random sample of 190 participants from the Pittsburgh Epidemiology of Diabetes Complications Study, a prospective cohort of childhood-onset type 1 diabetes mellitus, received radiographs of their ankles and feet at the 4-year follow-up examination (1990-1992) and was followed up for approximately 6 years. At the 10-year examination, 121 of these individuals received an electron beam tomography scan. Male sex (odds ratio [OR] = 12.72, $P < .0001$), diabetes duration (OR = 4.53, $P < .0001$), and autonomic neuropathy (AN; OR = 5.92, $P = .007$) independently increased the odds of LEAC. Controlling for other known risk factors (duration and high-density lipoprotein cholesterol), we found that LEAC correlated with the presence of CAC 6 years later (OR = 1.12, $P = .03$), although adjusting for neuropathy attenuated this relationship ($P = .08$). LEAC also independently predicted AN but not the onset of other diabetes complications. Although arterial calcification in the lower extremities and the heart share many of the same risk factors, LEAC is an independent correlate of the later presence of CAC and AN. Thus, factors related to the calcification process in addition to vascular risk factors may play a role in determining the extent of CAC.

1. Introduction

Individuals with type 1 diabetes mellitus have been shown to have up to a 10-fold increased risk for coronary artery disease (CAD) and mortality [1,2]. Lower-extremity arterial calcification (LEAC) is also common and has been shown to be associated with many traditional CAD risk factors and to CAD itself [3-6]. In diabetes, LEAC has also been related to renal failure and early mortality [7,8]. Coronary artery calcification (CAC) has previously been cross-sectionally correlated with CAD events in individuals with type 1 diabetes mellitus [9], and as such could potentially serve as an early marker of CAD. However, little is known concerning the association of LEAC with CAC and to what extent this may reflect shared risk factors. Moreover, as LEAC occurs mainly in the medial wall (Mönckeberg sclerosis) and CAC is thought to reflect plaque calcification, any association may also reflect the calcification process in general. Few, if any, studies to date have examined the relationship of LEAC with CAC in type 1 diabetes mellitus and compared their respective risk factors.

This analysis sought to identify risk factors associated with LEAC and to determine its relationship to the later presence of CAC in a cohort of individuals with type 1 diabetes mellitus in the setting of traditional risk factors. We also examined the relationship of LEAC to the development of other diabetes complications.

2. Research design and methods

Subjects for the analysis were participants of the Pittsburgh Epidemiology of Diabetes Complications (EDC) study. The EDC study, a 10-year prospective follow-up study of childhood-onset type 1 diabetes mellitus, has been previously described in detail [10]. Briefly,

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participants were diagnosed (or seen within 1 year of diagnosis) between 1950 and 1980, before their 17th birthday, at the Children's Hospital of Pittsburgh. This population has been shown to be representative of the type 1 diabetes mellitus population in Allegheny County, Pennsylvania [11]. Six hundred fifty-eight subjects met eligibility criteria and were first examined for the EDC study between 1986 and 1988. During the third biennial examination (1990-1992), a random subgroup of 190 participants had radiographs taken of their ankles and feet. During the 10-year follow-up examination (1996-1998), electron beam tomography (EBT) screening was initially (June 11, 1997) made available to all attending participants aged 30 years or older, and subsequently (October 15, 1997) to all participants aged 18 years or older. A total of 304 participants underwent EBT screening [9], including 121 who had previously undergone radiographs to look for LEAC. The third biennial examination (1990-1992) was considered as baseline for the present analysis.

2.1. Definition of risk factors and outcome measures

LEAC was graded as 0, absent; 1, barely visible; 2, specific outline; or 3, very dense (>2 cm) at 6 locations, namely, in the tibialis anterior, dorsalis pedis, and tibialis posterior arteries at the ankle level, and the plantaris, metatarsal, and digital arteries in the foot. LEAC was independently assessed by 2 observers (TJO, SJW). In case of disagreements, the observers discussed the x-rays together and agreed on a score. These x-rays were also independently reviewed by investigators in the Netherlands (Dr Ronald Stolk and Dr Willemijn Klein). A composite LEAC score was calculated using a cumulative index (summation) of the scores from all of the 12 scoring locations on both of the lower limbs. Only linear calcification in the ankle x-rays, the characteristic of medial wall arterial sclerosis, was included in the LEAC score [12-15]. Scorer agreement (Netherlands vs Pittsburgh) for the cumulative index score was moderate (Spearman $\rho = 0.66$, $P < .0001$). LEAC was further quantified by dichotomizing the scores as "any LEAC" or "no LEAC" (κ statistic for the Netherlands vs Pittsburgh interobserver agreement = 0.89, $P < .0001$). To maximize accuracy, sample size, and information provided by the LEAC score, an ordinal variable was created by categorizing the distribution of the composite LEAC score into 3 groups. Those with no LEAC (n = 56) composed the lowest group. A median split was then used to divide the remaining individuals into 2 groups, one with a composite LEAC score of 1 to 6 (n = 29) and a third group with LEAC values of 7 to 24 (n = 35). All analyses were based on the radiograph scoring done in Pittsburgh.

CAC was assessed via EBT using a GE-Imatron ultrafast computed tomography scanner (GE-Imatron, San Francisco, CA). Scans were triggered by electrocardiogram (ECG) signals at 80% of the R-R interval and obtained in 3-mm contiguous sections of the heart. CAC was calculated by the Agatston method of scoring, using the number, area, and peak Hounsfield units of calcified lesions [16]. A lesion score was calculated by multiplying the density score and the area, and a total calcium score was determined by adding up each of these scores for all slices.

All other complications and risk factors were assessed at the same time as the LEAC (ie, 1990-1992) and were assessed as correlates of CAC (1996-1998). CAD was defined as EDC physician-diagnosed angina, myocardial infarction confirmed by Q waves on an ECG (Minnesota codes 1.1 or 1.2) or through hospital records, angiographic stenosis of 50% or higher, coronary artery bypass surgery, angioplasty, or ischemic ECG changes (Minnesota codes 1.3, 4.1-4.3, 5.1-5.3, and 7.1). Hypertension was characterized as a blood pressure of 140/90 mm Hg or higher or current treatment with antihypertensive medications. Glycosylated hemoglobin (HbA_1) level was measured by automated high-performance liquid chromatography (Diamat, BioRad, Hercules, CA). Cholesterol and triglycerides were measured enzymatically [17,18]. High-density lipoprotein (HDL) cholesterol was determined by using a modified [19] heparin and manganese chloride precipitation technique of the Lipid Research Clinics method [20]. Low-density lipoprotein (LDL) cholesterol was calculated by using the Friedewald equation [21]. Non-HDL cholesterol was calculated as total minus HDL cholesterol. Plasminogen activator inhibitor 1 (PAI-1) concentrations were determined as previously described [22] by an enzyme-linked immunosorbent assay procedure (American Bioproducts, Parsippany, NJ) [23]. Fibrinogen levels were measured by using a biuret colorimetric procedure and a clotting method.

Serum and urinary albumin were measured by immunonephelometry [24,25], and creatinine level was assayed by an Ectachem 400 Analyzer (Eastman Kodak, Rochester, NY). Overt nephropathy (ON) was defined as albumin excretion rate (AER) greater than 200 μg/min in 2 of 3 timed urine collections or, in the absence of urine, a serum creatinine level greater than 153 μmol/L (>2 mg/dL), or renal failure or renal transplantation. Distal symmetric polyneuropathy was assessed according to the signs and symptoms identified in the Diabetes Control and Complications Trial protocol [26] and was confirmed by using a Vibraton II (Physitemp Instruments, Clifton, NJ) at or after the 4-year follow-up examination (confirmed distal symmetric polyneuropathy [CDSP]) by the presence of an age-specific vibratory threshold above the reference range. Autonomic neuropathy (AN) was assessed by measuring heart rate response to deep breathing (expiration-inspiration ratio). A ratio of less than 1.1 was considered abnormal [27]. Proliferative retinopathy (PR) was assessed by stereo fundus photography using the Arlie House System of classification [28] or a history of laser treatment for proliferative disease. Lower-extremity arterial disease (LEAD) was defined as an ankle-brachial index less than 0.9 [29], or claudication, or by a history of amputation for a vascular cause.

Table 1
Univariate risk factors associated with any lower-extremity ankle calcification (the Pittsburgh EDC study 1990-1992)

Characteristics	LEAC	No LEAC	OR (95% CI)	Spearman ρ
n	64	57	–	–
Age (y)	36.6 ± 6.0	28.7 ± 6.3	4.12 (2.43-6.98)****	0.49****
Diabetes duration (y)	27.9 ± 6.6	19.6 ± 6.7	3.80 (2.31-6.27)****	0.48****
% Male	57.8 (37)	28.1 (16)	3.51 (1.64-7.52)**	–
% Hypertension	31.3 (20)	10.5 (6)	3.86 (1.43-10.48)**	–
% Ever smoked (n = 63, 56)	36.5 (23)	32.1 (18)	1.21 (0.57-2.60)	–
Smoking now (%, n) (among ever smokers)	26.1 (6)	55.6 (10)	0.28 (0.08-1.05)	–
% CAD	26.6 (17)	10.5 (6)	3.07 (1.12-8.45)*	–
% ON	32.8 (21)	12.3 (7)	3.49 (1.35-9.00)**	–
% CDSP (n = 63, 56)	33.3 (21)	7.1 (4)	6.50 (2.07-20.40)**	–
% PR	56.3 (36)	28.6 (16)	3.21 (1.50-6.88)**	–
% AN (n = 61, 54)	41.0 (25)	20.4 (11)	2.71 (1.18-6.26)*	–
% LEAD	12.5 (8)	10.5 (6)	1.21 (0.39-3.74)	–
BMI (kg/m^2)	25.1 ± 3.2	23.9 ± 3.5	1.47 (0.999-2.16)	0.20*
SBP (mm Hg)	119.8 ± 18.6	109.8 ± 14.7	1.94 (1.25-3.01)**	0.28**
DBP (mm Hg)	73.2 ± 9.5	68.9 ± 7.7	1.69 (1.14-2.51)**	0.25**
HbA_1 (%, n = 62, 56)	10.7 ± 1.7	10.5 ± 1.4	1.14 (0.79-1.64)	0.06
Total cholesterol (mg/dL, n = 63, 57)	192.4 ± 38.2	179.6 ± 37.6	1.42 (0.97-2.07)	0.18
HDL-C (mg/dL, n = 63, 57)	51.5 ± 9.5	55.3 ± 12.1	0.69 (0.47-1.02)	−0.17
LDL-C (mg/dL, n = 55, 51)	118.3 ± 31.0	107.1 ± 28.8	1.47 (0.98-2.19)	0.15
Non–HDL-C (mg/dL, n = 63, 57)	140.9 ± 38.1	124.3 ± 36.3	1.60 (1.08-2.37)*	0.26**
Triglycerides (mg/dL, n = 55, 51)[a]	93.1 ± 64.5	74.4 ± 35.8	1.51 (0.94-2.42)	0.15
BDI (n = 61, 53)[b]	7.9 ± 7.1	5.5 ± 6.9	1.44 (0.96-2.15)	0.21*
Fibrinogen (mg/dL, n = 62, 57)[a]	315.2 ± 105.3	286.6 ± 87.5	1.37 (0.93-2.02)	0.14
WBC count (× 10^3, n = 63, 56)[a]	7.4 ± 2.7	7.2 ± 2.2	1.11 (0.76-1.60)	0.01
Serum creatinine (mg/dL, n = 63, 57)[b]	1.2 ± 0.94	0.90 ± 0.37	3.19 (1.19-8.57)*	0.35****
PAI-1 (mg/dL, n = 62, 55)[a]	23.5 ± 14.9	24.7 ± 15.7	0.92 (0.64-1.33)	−0.05
AER (μg/min)[b]	267.7 ± 600.1	150.8 ± 422.9	1.28 (0.85-1.93)	0.25**

Data are means ± SD or % (n). ORs (95% confidence intervals [CIs]) are per 1 SD increase in continuous variables. SBP indicates systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; WBC, white blood cell.

[a] Natural log-transformed.

[b] Wilcoxon rank sum test.

* $P \leq .05$.

** $P \leq .01$.

*** $P \leq .001$.

**** $P \leq .0001$.

Before each biennial clinic visit, participants were sent questionnaires concerning demographic information, health care, medical history, and physical activity. Smoking status (ever/never or current) and Beck Depression Inventory (BDI) [30] were self-reported.

3. Statistical analysis

Univariate associations of risk factors to LEAC or CAC score were evaluated by using the χ^2 test or the Student t test. Continuous variables were normalized by using logarithmic transformation where appropriate (ie, triglyceride level, fibrinogen concentration, white blood cell count, PAI-1, and BDI score), or, if this was not possible (ie, serum creatinine level and AER), the Wilcoxon rank sum test was used. Results were considered significant at P less than .05. The Cochran-Armitage test for trend was used to examine the possibility of a dose-response effect in the relationship of LEAC to CAC.

Because of the high number of subjects with no calcification (n = 66), a two-stage regression approach was used to examine multivariate correlates of CAC. In the first stage, multiple logistic regression was used to assess the development of CAC (any vs none). All univariate significant correlates of the presence of any CAC were allowed to enter the stepwise selection process and variables were required to have a P value of .10 or less to remain in model 1. Model 2 further allowed for LEAC status, whereas subsequent models also allowed for the presence of diabetes complications one at a time. In the second stage, multiple linear regression was used to identify the factors associated with higher amounts of CAC, conditional upon having a CAC score greater than zero. LEAC was modeled as a categorical variable with 3 levels. The relationship of LEAC to the development of several diabetes complications (including AN, CAD, CDSP, PR, ON/renal failure, and mortality) was modeled by using Cox proportional hazard models with entry and exit criteria of P of .05 or less and P of .10 or less, respectively. Duration of diabetes was forced into all statistical models. The Akaike information criterion (AIC) was used to select the best model. Statistical analyses were performed with

Table 2
Independent risk factors (1990-1992) that are associated with the presence of LEAC: multiple logistic regression analysis (n = 105, 55 cases) (the Pittsburgh EDC study)

Variable	OR (95% CI)	*P*
Duration of diabetes (y)	4.53 (2.32-8.85)	<.0001
Sex (male)	12.72 (3.66-44.27)	<.0001
AN status	5.92 (1.62-21.60)	.007
AIC	99.379	

Risk factors made available for the stepwise modeling process included those significant in a univariate fashion (diabetes duration, sex, BMI, hypertension, HDL, non-HDL, CAD, ON, CDSP, PR, AN, serum creatinine level). Risk factors were required to be significant in the model at the $P < .10$ level. The OR for diabetes duration is presented per 1 SD increase (SD = 7.84 years).

SAS statistical software version 9.1 for windows (SAS Institute, Cary, NC).

4. Results

CAC scans were introduced during the 10-year examination cycle (June 11, 1997) because of a sudden availability of funding, initially to all those aged 30 years or older and subsequently (October 15, 1997) to all younger individuals (all aged 18 years or older). Thus, at the time of the original LEAC determination, persons with a subsequent EBT were older than those without a scan. They were also more likely to be women, less likely to smoke, and had a better lipid profile and HbA_1 levels. They were also more likely to have AN (not shown). However, there was little self-selection, scanning being determined primarily by funding and age. Approximately 79% of persons older than 30 years attending the exam had an EBT when it was available. At follow-up (when EBT was made available), those with and without an EBT did not differ except for an older age, a lower prevalence of smoking, a higher prevalence of AN, and lower systolic blood pressure in those with an EBT.

4.1. LEAC risk factor profile

Table 1 shows the cross-sectional correlates of LEAC at baseline (1990-1992). Subjects with LEAC were significantly older, had a longer duration of diabetes, and were

Table 3
Baseline risk factors (1990-1992) by the subsequent presence of CAC (the Pittsburgh EDC study 1996-1998)

Characteristics	CAC	No CAC	OR (95% CI)	Spearman ρ
n	55	66	–	–
Age (y)	37.2 ± 6.2	29.2 ± 6.0	4.25 (2.50-7.24)****	0.56****
Duration of diabetes (y)	28.4 ± 6.8	20.3 ± 6.6	3.44 (2.15-5.51)****	0.52****
% Male	47.3 (26)	40.9 (27)	1.30 (0.63-2.67)	–
% LEAC	74.6 (41)	34.9 (23)	7.01 (3.01-10.33)****	–
Composite LEAC score[a]	6.6 ± 6.2	2.3 ± 4.3	1.19 (1.09-1.30)****	0.44****
% Hypertension	34.6 (19)	10.6 (7)	4.45 (1.70-11.63)**	–
% Ever smoked	39.6 (21)	30.8 (20)	1.48 (0.69-3.16)	–
Smoking now (%, n) (among ever smokers)	42.9 (9)	35.0 (7)	1.39 (0.46-4.92)	–
% CAD	25.5 (14)	13.6 (9)	2.16 (0.85-5.47)	–
% ON	34.6 (19)	13.6 (9)	3.34 (1.36-8.19)**	–
% CDSP	40.0 (22)	4.7 (3)	13.56 (3.78-48.68)****	–
% PR	63.6 (35)	26.2 (17)	4.94 (2.27-10.78)****	–
% AN	49.1 (26)	16.1 (10)	5.01 (2.11-11.89)***	–
% LEAD	16.4 (9)	7.6 (5)	2.39 (0.75-7.60)	–
BMI (kg/m^2)	25.4 ± 3.7	23.9 ± 3.0	1.56 (1.06-2.29)*	0.19*
SBP (mm Hg)	121.3 ± 20.0	109.9 ± 13.1	2.00 (1.33-3.00)***	0.31***
DBP (mm Hg)	73.1 ± 9.5	69.5 ± 8.1	1.57 (1.04-2.38)*	0.16
HbA_1 (%)	10.6 ± 1.5	10.6 ± 1.5	1.03 (0.69-1.56)	0.03
Total cholesterol (mg/dL)	193.9 ± 37.6	180.1 ± 38.2	1.46 (0.99-2.14)	0.18*
HDL-C (mg/dL)	51.1 ± 8.8	55.0 ± 12.2	0.67 (0.44-1.01)	−0.13
LDL-C (mg/dL)	119.5 ± 27.9	108.2 ± 31.3	1.51 (0.98-2.32)	0.21*
Non–HDL-C (mg/dL)	142.7 ± 39.6	125.1 ± 35.1	1.65 (1.11-2.45)*	0.23**
Triglycerides (mg/dL)[b]	96.3 ± 68.7	75.5 ± 37.1	1.78 (0.97-3.25)	0.13
BDI[a]	8.1 ± 7.4	5.7 ± 6.7	1.42 (0.97-2.08)	0.21*
Fibrinogen (mg/dL)[b]	325.1 ± 104.8	281.9 ± 87.7	1.61 (1.07-2.41)*	0.22*
WBC count (10^3)[b]	7.8 ± 3.0	6.9 ± 1.8	1.44 (0.96-2.17)	0.12
Serum creatinine (mg/dL)[a]	1.3 ± 1.0	0.91 ± 0.26	2.84 (1.22-6.64)*	0.22*
PAI-1 (mg/dL)[b]	24.6 ± 14.9	23.6 ± 15.6	1.08 (0.70-1.68)	0.06
AER ($\mu g/min$)[a]	281.4 ± 596.4	155.3 ± 454.6	1.41 (0.83-2.38)	0.28**

Data are means ± SD or % (n). ORs (95% CIs) are per 1 SD increase in continuous variables.
[a] Wilcoxon rank sum test.
[b] Natural log-transformed.
* $P \le .05$.
** $P \le .01$.
*** $P \le .001$.
**** $P \le .0001$.

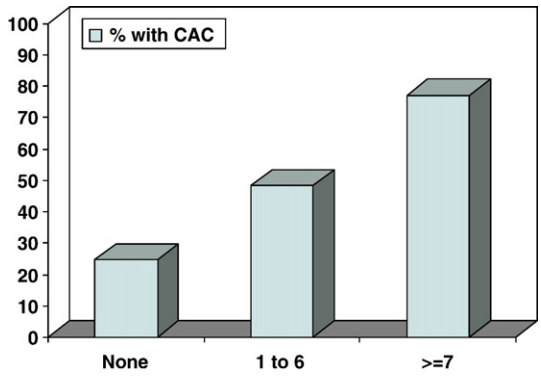

Fig. 1. Prevalence of CAC by composite LEAC score (n = 121). The Pittsburgh EDC study. Cochran-Armitage test for trend, $P < .0001$.

more likely to be men. They were also more likely to have all of the major complications except for LEAD prevalence. Individuals with LEAC also displayed a poorer lipid profile, had higher blood pressures, and were more likely to be hypertensive. Inflammatory markers were not increased in those with LEAC although BDI scores were. There was no difference in HbA_1 or smoking status.

One hundred five individuals had complete information for all covariates considered in multivariable analyses. In a stepwise multiple logistic regression process that controlled for duration of diabetes, male sex (OR = 12.72, $P < .0001$), and AN (OR = 5.92, $P = .007$) were found to independently increase the odds of a subject having LEAC (Table 2).

4.2. CAC correlates

The comparisons between the risk factors (measured in 1990-1992) of subjects who 6 years later (1996-1998) were found to have CAC and those who did not (mean follow-up time = 6.2 ± 0.70 years) are presented in Table 3. Subjects who had CAC later were significantly older and had a longer duration of diabetes; however, there were no differences in sex, smoking status, and HbA_1. They had higher blood pressures and were more likely to be hypertensive and have major microvascular complications, although no significant differences were seen for either CAD or LEAD, which had a lower prevalence. The presence of CAC was further distinguished by a somewhat more adverse lipid profile 6 years earlier. Of particular note was the strong association between LEAC and CAC 6 years later (Spearman $\rho = 0.44$, $P < .001$). This is shown graphically in Fig. 1.

4.3. Multivariable correlates of CAC using LEAC

In stepwise multiple logistic regression (n = 105), LEAC was significantly associated with the later presence of CAC (Table 4, model 1). Other factors considered were diabetes duration, sex, body mass index (BMI), HDL and non-HDL cholesterol levels, hypertension, fibrinogen concentration, serum creatinine level, and ON status. When additional models were constructed further adjusting for the presence of diabetes complications (one at a time), the effect of LEAC was not altered with the exception of models including the 2 neuropathy measures, namely, CDSP and AN, where the effect of LEAC was attenuated ($P = .08$). When compared with subjects with no LEAC, the group with the most LEAC (composite LEAC score ≥ 7) had a 6-fold increased risk for the later presence of CAC (OR = 6.31, $P = .003$). In the subgroup of subjects with later CAC (n = 55), stepwise multiple linear regression revealed that LEAC was not a significant independent correlate of the extent of CAC (not shown). However, in this subgroup, the nature of the relationship between LEAC and CAC score remained of a positive nature (Spearman $\rho = 0.21$, $P = .12$).

Cox proportional hazard modeling was also used to look at the 6-year incidence of diabetes complications between the 4-year and the 10-year biennial examination. Controlling for duration of diabetes and other risk factors, LEAC showed no independent effect on the incidence of CAD (n = 32) or PR (n = 27). However, LEAC was independently related to the incidence of AN (n = 29, p = .03). To further explore the link with AN, further assessments of AN (expiration-inspiration ratio <1.1, difference of supine to standing systolic blood pressure >10 mm Hg, ratio of maximal R-R interval at the 30th beat to the shortest R-R interval at the 15th beat after standing ≤1.04) available at follow-up were treated as outcomes, and LEAC from the biennial examination during 1990-1992 was found to be

Table 4
Independent baseline risk factors (1990-1992) that are associated with the subsequent presence of CAC (1996-1998): multiple logistic regression analysis (n = 105; 48 with CAC) (the Pittsburgh EDC Study)

Variable	Model 1	Model 2	Model 3
Diabetes duration (y)	4.44 (2.31-8.52), $P < .0001$	4.06 (2.08-7.93) $P < .0001$	4.75 (2.21-10.22), $P < .0001$
BMI (kg/m^2)	Not selected	1.94 (0.96-3.94), $P = .06$	2.18 (1.08-4.43), $P = .03$
HDL-C	0.52 (0.29-0.93), $P = .03$	0.56 (0.28-1.10), $P = 0.09$	0.46 (0.23-0.95), $P = .04$
LEAC category	1.12 (1.01-1.24), $P = .03$	1.10 (0.99-1.22), $P = 0.08$	1.10 (0.99-1.22), $P = 0.08$
CDSP	Not available	20.55 (3.00-140.67), $P = .002$	Not available
AN	Not available	Not available	10.79 (2.64-44.07), $P = .0009$
AIC	102.379	90.764	91.441

Values are presented as OR (95% CI), *P*. Model 1 allowed for diabetes duration, sex, BMI, hypertension, HDL, non-HDL, fibrinogen, serum creatinine level, ON, and LEAC category. Model 2 allowed for variables in Model 1, in addition to CDSP. Model 3 allowed for variables included in Model 1, in addition to AN. ORs are presented per 1 SD increase for continuous variables.

univariately related to the expiration-inspiration ratio (P = .0003) and to the difference of supine to standing systolic blood pressure (P = .08) but not to the 30:15 ratio (P = .50).

5. Discussion

This article examined the risk factor profile of LEAC and its relationship with the later presence of CAC by taking known CAD risk factors into account in a cohort of participants with type 1 diabetes mellitus. The results demonstrated an increasing prevalence of CAC 6 years later based on the amount of LEAC they had at baseline. This relationship was independent of all other known correlates of CAC in this cohort, although it was attenuated when controlling for neuropathy status.

Interestingly, the risk factors that were cross-sectionally associated with the presence of LEAC also, for the most part, correlated with the later presence of CAC, at least in a univariate fashion. Thus, subjects with high LEAC who later show CAC had several common traits: they were more likely to be older, hypertensive, have neuropathy, and have a poorer lipid profile. These similarities between the risk factor profiles of subjects with LEAC and subjects with CAC might suggest a common pathogenesis for arterial calcification in both locales. Conversely, although a much higher proportion of participants with LEAC was male, this male preponderance was not observed in CAC. This leveling of sex differences in the presence of calcium in the coronary arteries in type 1 diabetes mellitus compared to nondiabetic populations has been shown previously [9,31,32]. However, it is difficult to draw conclusions from these data on whether the excess male presence in the LEAC group denotes an early sex difference in calcification overall that later disappears or whether sex differences exist in the calcification of the lower extremities but not the coronary arteries.

LEAC remained a correlate of the later presence of CAC independent of most risk factors, indicating that LEAC may explain CAC variation beyond standard CAD risk factors. Its effect, however, was attenuated after adjustment for neuropathy status. Previous studies have suggested that AN is a key determinant of medial calcification in patients with diabetes [33,34] and that it is associated with cardiovascular risk factors [35]. Thus, it could be argued that LEAC is merely a marker of neuropathy, and not itself an independent risk factor. Our data would suggest otherwise, as LEAC did improve the model fit. Furthermore, this issue was also assessed by Mayfield et al [34] who showed that AN could not entirely explain the excess mortality, amputation, and ulceration in persons with medial arterial calcinosis. This important observation, in addition to our results, may suggest that there might be more to the LEAC-CAC association beyond a shared link with neuropathy. Curiously, LEAC was not associated with the extent of CAC among individuals with at least some CAC, although the small sample size may limit power in these analyses.

Little research is available that examines the relationship between different locales of arterial calcification. However, some data are available that look at the relationship of peripheral vascular disease and CAD. In an earlier EDC analysis by Olson et al [9], peripheral vascular disease (defined as ABI <0.8, history of claudication, amputation from vascular cause, or ankle-brachial difference of ≥ 75 mm Hg) was found to be cross-sectionally related to CAC in both men and women. In this analysis, a high ABI was used as a surrogate marker of LEAC and was found to be significantly related to CAC. These previous results are strengthened by our analysis, which used a stronger marker of actual LEAC instead of surrogate markers. The study by Iribarren et al [36] showed an increasing rate of peripheral vascular disease in both men and women who also had aortic arch calcification, although the difference did not reach statistical significance.

Despite the modest sample size used in this analysis (n = 121), the extended follow-up period (6.2 $\pm$ 0.70 years) lends strength to the results. The scoring methodology used for the quantification of LEAC was more quantitative than the scoring system used in most of the current literature that classifies calcification as either “patchy”/intimal or linear in nature [13]. Conversely, the presence of calcium in the coronary arteries is an indication of intimal atherosclerosis [37]. The scarcity of reports demonstrating CAC being present in the absence of atherosclerotic plaque, in addition to the strong pathophysiologic data demonstrating that EBT represents intimal calcification [38-40], further shows that EBT scans do indeed measure atherosclerotic plaque.

The lack of any strong associations between LEAC and the incidence of diabetes complications is in contrast to some findings that have suggested that LEAC is prospectively associated with increased mortality [4], amputations [4,15,41], nephropathy [4,5], retinopathy [4,5], and CAD [4,15]. However, the modest size of this study population may limit our power in these analyses. Other limitations include the determination of LEAC and CAC status at different time points, allowing only for inferences regarding correlation but not prediction. Different methodologies were used for detecting calcium in the lower extremities and the coronary arteries. As EBT is more sensitive compared to plain films, it is possible that the calcification detected in the lower extremities represents more severe disease compared with the calcification detected in the coronary arteries. Furthermore, although we tried to standardize the ankle x-ray data and plain film acquisition by having the same technician, whenever possible, obtain x-rays (and by seeking consensus of the 2 observers for all x-rays), in the cases where different technicians were involved it is possible that different tissue depths and findings could have occurred. It is likely, however, that such variation would only introduce noise and not systematic bias. Finally, when compared with participants without an EBT, those with a scan showed some baseline differences, notably age, as initially, scans were offered to those aged 30 years or older.

However, the differences, with the exception of older age, were less marked comparing those with and without an EBT at the examination cycle when scans were offered. Thus, our results may not be fully generalizable to the total type 1 diabetes mellitus population and may have, to a small extent, underestimated true coronary calcification. Nonetheless, it is unlikely that these differences may have led to spurious associations between LEAC and CAC within the group studied.

There are a number of interpretations of the results of this study, beyond the observation that the risk factors for LEAC and CAC are similar and that LEAC may be a useful correlate of CAC. The nature of this association may simply reflect the fact that atherosclerotic risk factors predict both peripheral and coronary calcification despite the former (LEAC) reflecting medial wall calcification of the Mönckeberg type and the latter reflecting atherosclerotic plaque. The second interpretation is that the association of LEAC and CAC reflects an increased susceptibility to calcification per se. This would seem a possibility worthy of future research and may help to refine the role of CAC in CAD prediction. A number of studies have reported on the association between specific gene variants and CAC [42-47]. Although results are not always consistent, certain of these genes may also predict cardiovascular disease [48-50]. If a subgroup of individuals have CAC largely on the basis of a tendency to calcify, as can generally be suggested by these results, rather than be a reflection of atherosclerosis per se, the identification of this subgroup would help refine the value of CAC as a predictor of CAD events because it could identify some potential false positives.

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