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Greater progression of coronary artery calcification is associated with clinically relevant cognitive impairment in type 1 diabetes

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HIGHLIGHTS

- Coronary artery calcification (CAC) is associated with cognitive impairment in middle-aged type 1 diabetes individuals.
- CAC progression is more informative than initial CAC in predicting impaired cognition in type 1 diabetes.
- CAC and high ankle-brachial index are independently associated with cognitive impairment in type 1 diabetes.

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ABSTRACT

Background and aims: We assessed the predictive role of coronary artery calcification (CAC) in clinically relevant cognitive impairment in 148 middle-aged individuals with childhood-onset type 1 diabetes (T1D) from the Pittsburgh Epidemiology of Diabetes Complications (EDC) Study.

Methods: Baseline CAC was measured in 1996–98 and repeated 4–8 years later. Per extensive neuropsychological testing in 2010–15, 28% (41/148) of participants met the study definition of clinically relevant cognitive impairment (two or more of 7 select test scores ≥1.5SD worse than demographically appropriate published norms). Logistic regression models with backward selection were constructed for statistical analysis.

Results: Mean age and T1D duration at first CAC measure were 37 and 29 years, respectively. A greater burden of initial CAC was associated with cognitive impairment determined 14 years later. Compared to Agatston score = 0, odds ratio (OR) and 95% confidence intervals (CI) of 0 < −100, 100 < −300 and > 300 were 1.4 (0.6, 3.6), 2.3 (0.6, 9.7), and 7.9 (1.6, 38.5), respectively. With both initial and progression of CAC in the multivariable model, backward selection retained only CAC progression, showing it was significantly associated with cognitive impairment (OR [95% CI]: 1.7 [1.1, 2.9]). In those with an initial CAC > 0, CAC density was marginally, inversely, associated with cognitive impairment when controlling for CAC volume (OR [95%CI]: 0.3 (0.1, 1.2), p value = 0.078).

Conclusions: Greater CAC burden was associated with clinically relevant cognitive impairment in middle-aged adults with childhood-onset T1D. CAC progression appears to be a more powerful predictor than initial calcification.

1. Introduction

Dementia has become the greatest global public health challenge in modern society, and the number affected is projected to triple from 2015 to 2050 [1]. Impaired cognitive function is highly prevalent in people with type 1 diabetes [2]. The Pittsburgh Epidemiology of Diabetes Complications (EDC) Study reported a 28% prevalence of clinically relevant cognitive impairment in middle-aged (mean age: 49 years) adults with childhood-onset type 1 diabetes [2], being comparable with that of the general population aged 85 years or older [3]. The pathophysiological basis for the earlier-than-expected occurrence of cognitive dysfunction in people with type 1 diabetes remains unclear, yet its associations with microvascular complications (diabetic retinopathy [4] and diabetic neuropathy [5,6]) and extreme ankle-brachial index (ABI) values suggest a parallel vascular pathogenesis in the brain as well as in other parts of the body [7].

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Numerous studies have documented a link between cognitive function and cardiovascular disease and associated risk factors in the general population [8]. Coronary artery calcification (CAC), an established marker of subclinical atherosclerosis in the heart and a predictor of cardiovascular events [9], has been shown to be independently associated with poor cognition and dementia in the general population [10–12].

Diabetes is known to carry a greater burden of vascular calcification, leading to an accelerated vascular aging process, which may, at least partially, explain the increased cardiovascular risk in this patient population. To our knowledge, however, few studies has examined the role of CAC in cognition impairment in those with type 1 diabetes [13]. Thus, the primary aim of this study was to evaluate the relationship of CAC with later clinically relevant cognitive impairment among middle-aged individuals with childhood-onset type 1 diabetes. Initial CAC, annual progression rate, and CAC density were all evaluated.

Vascular calcification occurs in two distinct forms, depending on the location: intima or medial wall. Though CAC may reflect both intimal and medial calcification, existing evidence suggested it mainly represented intimal calcification [14]. Medial arterial calcification is a feature of diabetes, which is characterized by high ankle blood pressure, reflecting poor compressibility of the artery. A high ABI associated with medial calcification is already well established [15]. The secondary aim was to assess the relative roles of CAC and high ABI in the association with impaired cognition. As the CAC was only shown having a modest effect on poor cognition in prior work [10–12], we hypothesized that CAC and high ABI were independently associated with cognitive impairment.

2. Study population and methods

2.1. Study population

The Pittsburgh EDC cohort is an ongoing, prospective study of now middle-aged adults diagnosed with childhood-onset type 1 diabetes (diagnosed before age 17 years). This population has previously been described in detail [16]. In brief, 658 eligible participants were examined between 1986 and 1988, with the 30th year of follow-up currently ongoing. Participants were assessed biennially by surveys and using highly standardized methods by examination for the first 10 years and again in 18, 25 and 30 years. The cohort has been shown to be epidemiologically representative of the type 1 diabetes population in Allegheny County, Pennsylvania [17]. The University of Pittsburgh Institutional Review Board approved the study protocol.

At the EDC 10-year follow-up examination (1996–1998), electron beam computed tomography (EBCT) scans were conducted to measure CAC for all participants aged ≥18 years; some repeated the scans 4–8 years later (2000–2006). During 2010–2015 (at the EDC 22- and 25-year follow-ups), all locally dwelling EDC participants were invited to participate in an ancillary neurocognitive study to evaluate cognition. A total of 148 participants underwent both of the CAC and the neurocognitive tests and were eligible in the present analysis of CAC and cognitive impairment. The mean (standard deviation, SD) time interval between initial CAC and later cognitive tests was 14.0 (3.5) years (range: 4.7–19.2 years). Of these 148, 116 of them had repeated CAC scans and were included in the subgroup analysis of CAC progression.

2.2. Cognitive assessment

The cognitive assessment of the EDC study has been described in details elsewhere [2,18]. Briefly, extensive neurocognitive tests were performed to assess cognitive function, including verbal intelligence (North American Adult Reading Test [NAART]), learning and working memory (Rey Auditory Verbal Learning Tests, Rey-Osterrieth Complex Figure Delay Task [ROCF-Delay], and Four Word Short Term Memory [4WSTM]), executive function (Verbal Fluency F-A-S [FAS], Trails Making Test-part B [TMTB], Stroop Color-Word [Stroop-CW], and Letter/Number Sequence [LN Sequence]), psychomotor efficiency (Digit Symbol Substitution Test [DSST], Grooved Pegboard [GP], and Trail Making Test-part A [TMTA]), semantic fluency (Verbal Fluency Animals [Animals]), and visuo-construction skills (Rey-Osterrieth Complex Figure Copy Task [ROCF-copy]). Of these, individual with type 1 diabetes performed significantly worse than non-diabetes controls on the following seven tests: FAS, TMTB, DSST, GP, Stroop-CW, Animals, and ROCF-copy [2]. Clinically relevant cognitive impairment was defined as having two or more of these test scores ≥1.5 SD worse than demographically-appropriate published norms [19,20].

2.3. Assessment of coronary artery calcification (CAC)

CAC was measured using EBCT scans (GE-Imatron C-150 scanner, South San Francisco, CA, USA). Scans were triggered by electrocardiogram signals at 80% of the R-R interval and obtained in 3 mm contiguous sections of the heart. Calcification was quantified using the method described by Agatston et al. [21] and CAC volume was based on the isotropic interpolation method [22]. The area and density scores were obtained using the algorithms from the Multi-Ethnic Study of Atherosclerosis (MESA) study [23]. Specifically, the area score was obtained by dividing the volume by the scan slice thickness of 3.0 mm. The density was subsequently calculated by dividing the Agatston score by area score. The progression was determined as the annualized difference between the square root of baseline and square root of follow-up CAC score (annual CAC progression = [sqrt (follow-up CAC) - sqrt (baseline CAC)]/[t2-t1 in years]). This calculation was previously applied by Radford et al. [24]. CAC volume might be a better measure of progression as the Agatston score is determined using both CAC density and volume [25]. Our primary analysis of CAC progression was thus based on CAC volume. Progression in CAC Agatston score associated with incident CAD was also examined as Agatston score has been widely used.

2.4. Measurement of covariates

Information regarding demographic, physical covariates, biomedical tests, and diabetes complication status were collected at the time of first CAC measure. Demographic and medical history information was obtained through questionnaires. An ever smoker was defined as a person who had smoked at least 100 cigarettes in the lifetime. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. Blood pressure was measured using a random zero sphygmomanometer according to the Hypertension Detection and Follow-up Program protocol [26]. Hypertension was defined as a systolic blood pressure ≥140 mm Hg, a diastolic blood pressure ≥90 mm Hg, or the use of antihypertensive medications.

A Doppler blood flow detector was used to measure systolic blood pressure in the brachial, posterior tibial, and dorsalis pedis arteries to obtain ABI. An average of two readings greater than 1.3, or non-compressible, was defined as high ABI. The cut-off point of 1.3 were based on published work from this same cohort, showing ABI > 1.3 was highly correlated with medial arterial calcification by X-ray [15]. A meta-analysis documented ABI < 0.9 to be a marker of cognitive impairment and dementia [27]. However, only one participant in this analysis had an ABI < 0.9, which disallowed us to examine associations for extremely low ABI.

Glycosylated hemoglobin was obtained by the automated high-performance liquid chromatography (HPLC) (Diamat, BioRad, Hercules, CA, USA) at the time CAC was first assessed, and subsequently by the DCA 2000 analyzer (Bayer, Tarrytown, NY, USA). Results from the two methods were highly correlated (r = 0.95) [28]. The values were then converted to DCCT-aligned HbA1c using a regression equation derived from duplicate assays [28]. Total cholesterol and triglycerides were determined enzymatically [29,30]. High-density

Table 1
Clinical characteristics at the first measurement of CAC.[a]

Characteristics	Overall	CAC status at baseline	
	N = 148	No calcification (n = 80)	Prevalent CAC (n = 68)
Age, years	37.2 (7.0)	34.4 (6.8)	40.5 (5.7)[e]
Diabetes duration, years	28.6 (6.9)	26.3 (6.1)	31.4 (6.7)[e]
Age at diabetes onset, years	8.6 (4.0)	8.1 (4.1)	9.1 (3.9)
Female, % (n)	51.0 (76)	50.0 (40)	52.2 (36)
Years of education, years	14.9 (2.5)	15.0 (2.5)	14.8 (2.6)
Age at cognitive test, years	51.1 (7.0)	49.3 (6.8)	53.3 (6.7)[e]
ApoE (24, 34, or 44), % (n)	28.4 (42)	33.8 (27)	22.1 (15)
Ever smoker, % (n)	33.6 (50)	33.8 (27)	33.3 (23)
BMI, kg/m^2	25.3 (4.0)	24.1 (3.1)	26.7 (4.5)[e]
Systolic BP, mmHg	114.5 (16.5)	110.4 (12.1)	119.2 (19.4)[e]
Diastolic BP, mmHg	69.7 (11.0)	68.9 (8.6)	70.7 (13.3)
Hypertension, % (n)	18.1 (27)	8.8 (7)	29.0 (20)[e]
High ABI[b], % (n)	8.7 (13)	8.8 (7)	8.7 (6)
HbA1c, %	8.3 (1.4)	8.4 (1.3)	8.2 (1.5)
AER[c], μg/min	8.2 (4.6, 35.9)	7.5 (4.9, 21.3)	11.9 (4.2, 80.0)
HDL cholesterol, mmol/L			
Male	47.9 (11.0)	1.3 (0.3)	1.2 (0.3)
Female	63.2 (14.2)	1.7 (0.4)	1.5 (0.4)
Non-HDL cholesterol, mmol/L	130.7 (36.2)	3.3 (1.1)	3.5 (0.8)
Triglycerides[c], mmol/L	78.0 (58.0, 107.0)	0.8 (0.6, 1.3)	0.9 (0.7, 1.2)
Statin use, % (n)	7.5 (11)	0.0 (0)	15.9 (11)[e]
Distal symmetric polyneuropathy, % (n)	26.2 (39)	21.3 (17)	31.9 (22)
Proliferative retinopathy, % (n)	45.0 (67)	36.3 (29)	55.1 (38)[d]
CAD, % (n)	13.4 (20)	10.0 (8)	17.4 (12)
Baseline CAC			
Agatston[c]	0 (0, 31.5)	0 (0, 0)	42.6 (8.8, 188.9)[e]
Volume[c]	0 (0, 36.1)	0 (0, 0)	47.2 (14.4, 146.8)[e]
Density	1.4 (1.9)	0 (0, 0)	2.8 (1.8)[e]

ABI: ankle-brachial index, AER: urinary albumin excretion rate, ApoE: apolipoprotein E, BMI: body mass index, BP: blood pressure, CAC: coronary artery calcification, CAD: coronary artery disease, HbA1c: hemoglobin A1c, HDL cholesterol: high density lipoprotein cholesterol, SD: standard deviation.

[a] Categorical variable were presented as percentage (number) and continuous variables as mean (SD) or median (1st and 3rd quartiles).

[b] High ABI: ABI > 1.3.

[c] Logarithmically transformed before statistical testing.

[d] p value < 0.05 for the comparison between those with CAC = 0 and > 0.

[e] p value < 0.01 for the comparison between those with CAC = 0 and > 0.

lipoprotein (HDL) cholesterol was measured by a precipitation technique (heparin and manganese chloride) using a modified version of the Lipid Research Clinicals Clinics method [31]. Non-HDL cholesterol was calculated as total cholesterol minus HDL cholesterol. Urinary albumin was determined by immunonephelometry [32].

Diabetes complications, including coronary artery disease (CAD), proliferative retinopathy, and distal symmetric polyneuropathy (DSP), were evaluated at each follow-up using standard protocols as described previously [33].

2.5. Statistical analysis

Demographics and risk factors were compared between those with and without prevalent CAC (baseline CAC > 0 *vs.* = 0) and between those with and without clinically relevant cognitive impairment. The Chi-square test (or Fisher's Exact test) for dichotomous variables and the Student's *t*-test (or nonparametric Wilcoxon test) for continuous variables were used for these comparisons, as appropriate.

Logistic regression models were constructed to assess the associations of CAC measures and high ABI with clinically relevant cognitive impairment. Baseline CAC was examined in 4 categories (0, 0 < - 100, 100 < - 300 and > 300). Odds ratios (ORs) and 95% confidence intervals (CIs) were presented accordingly. Risk factors previously demonstrated to be important predictors of cognitive impairment in this type 1 diabetes group [2] and factors found to be significantly associated with the outcome events in univariable analyses were considered in the multiple regression analyses. Because age and diabetes duration were highly correlated (r = 0.84) in this cohort, only diabetes duration was used for the adjustment. As education attainment associated with cognitive impairment has been well established [34], year of education was adjusted in all the models.

To limit overfitting of a multivariable model, backward elimination was applied, allowing for a full set of covariates (gender, diabetes duration, years of education, age at cognitive test, apolipoprotein E4 [ApoE4] status [24, 34, or 44], ever smoking, BMI, hypertension, HbA1c, urinary albumin excretion rate[AER], HDL and non-HDL cholesterol, triglycerides, statin use, and presence of diabetes complications: CAD, DSP and proliferative retinopathy). Our model selection strategy was for a parsimonious model that was adjusted for potentially important confounding variables and had a lower Akaike Information Criterion (AIC) to be selected as the final model. Alternative multiple-adjusted models which allowed for different sets of risk factors are available in the Supplementary materials.

The log-likelihood ratio test was applied to assess the improvement of model fit for including CAC and/or high ABI.

Logistic regression with backward elimination was also applied for the tests of CAC density and CAC progression, respectively. Only participants with CAC over 0 were analyzed for CAC density (with controlling for log-transformed CAC volume) because plaque density could only be quantified in those with prevalent CAC [23]. The progression of CAC associated with clinically relevant cognitive impairment was examined in the subset with at least two CAC measures, with offering baseline CAC and other covariates (described above) in the model for backward selection.

Triglycerides and AER were log-transformed prior to statistical testing, given the highly skewed distribution of these variables. A 2-sided p < 0.05 was considered significant. All analyses were performed with SAS 9.3 (SAS Institute, Cary, NC).

Table 2
Associations of baseline CAC Agatston scores and high ABI with having clinically relevant cognitive impairment at follow-up.

Events = 41/N = 148	Model 1		Model 2		Model 3		Model 4 (backward selection[b], final model)	
Parameter	OR (95%CI)[a]	*p* value	OR (95%CI)[a]	*p* value	OR (95%CI)[a]	*p* value	OR (95%CI)[a]	*p* value
CAC Agatston scores								
0 (17/82)	ref		ref		ref		ref	
0 < −100 (12/44)	1.4 (0.6, 3.6)	0.173	1.3 (0.5, 3.3)	0.279	1.4 (0.5, 3.8)	0.286	1.4 (0.6, 3.6)	0.236
100 < −300 (4/11)	2.1 (0.5, 8.6)	0.787	1.5 (0.3, 6.8)	0.663	1.7 (0.4, 7.6)	0.734	2.3 (0.6, 9.7)	0.963
> 300 (8/11)	11.2 (2.4, 51.8)	0.008	7.2 (1.4, 36.7)	0.026	8.1 (1.5, 45.0)	0.033	7.9 (1.6, 38.5)	0.037
ABI								
≤1.3 (33/135)	ref		ref		ref		ref	
> 1.3 (8/13)	6.4 (1.7, 24.6)	0.007	6.1 (1.5, 24.1)	0.011	6.5 (1.5, 27.7)	0.011	6.0 (1.5, 24.3)	0.012
Year of education	0.6 (0.4, 0.9)	0.007	0.5 (0.4, 0.8)	0.007	0.6 (0.4, 0.9)	0.013	0.6 (0.4, 0.9)	0.010
Female	NA		1.1 (0.5, 2.6)	0.791	NA			
Age of cognition tests	NA		1.2 (0.7, 2.2)	0.474	NA			
Diabetes duration	NA		1.2 (0.7, 1.9)	0.673	NA			
HbA1c	NA		NA		1.2 (0.8, 1.9)	0.295		
BMI	NA		NA		0.8 (0.5, 1.3)	0.384		
Hypertension	NA		NA		1.6 (0.6, 4.8)	0.374		
Statin use	NA		NA		2.4 (0.4, 13.8)	0.334		
CAD	NA		NA		2.9 (0.9, 9.4)	0.073	3.4 (1.0, 10.8)	0.042
Proliferative retinopathy	NA		NA		1.1 (0.5, 2.7)	0.810		
AIC	*160.433*		*164.599*		*165.335*		*157.976*	

ABI: ankle-brachial index, AIC: Akaike information criterion, BMI: body mass index, CAC: coronary artery calcium, CAD: coronary artery disease, CI: confidence interval, HbA1c: hemoglobin A1c, NA: not available, OR: Odds ratio, SD: standard deviation.
Model 1: comprise CAC, high ABI, and year of education.
Model 2: Mode 1 + sex, age of cognition tests, and diabetes duration.
Model 3: Mode 1 + HbA1c, BMI, Hypertension, statin use, presence of CAD, and presence of proliferative retinopathy.
Model 4: Backward selection with a removal criterion of *p* value ≥ 0.10. In addition to baseline CAC and ABI, the year of education, sex, age at cognitive tests, diabetes duration, apolipoprotein E4 status, ever smoking, BMI, HbA1c, cholesterols (high density lipoprotein and non-high density lipoprotein), triglycerides, urinary albumin excretion rate, hypertension, proliferative retinopathy, distal symmetric polyneuropathy, and statin use were offered for model selection.
[a] Per SD higher value for continuous variables.
[b] CAC, high ABI, year of education and the existing CAD were retained in the final model after backward selection.

3. Results

Among the 148 participants at the first CAC measure (baseline of this analysis), the mean age and diabetes duration were 37.2 (range 18.3–56.1) and 28.6 (range 17.6–50.6) years, respectively. There were 46% (68/148) of participants with prevalent CAC at baseline. The time interval between two CAC scans were 5.5 (1.6) years. In those with baseline CAC = 0, 39% developed somewhat calcification during the follow-up. Compared to participants without CAC, those with prevalent CAC were older, had higher BMI and systolic blood pressure, were more likely to use statins, have hypertension and/or proliferative retinopathy (Table 1).

The neurocognitive test battery was conducted a mean (SD) of 14.0 (3.5) years after the first CAC measurement, with 41 (27.7%) participants meeting the definition of clinically relevant cognitive impairment. Compared with cognitively normal non-cases, cognitive impairment cases were less educated, older, with longer diabetes duration, and more likely to have a high ABI (> 1.3) and/or CAD (Supplementary Table 1).

The proportion of later cognitive impairment increased with increasing baseline CAC: at the follow-up, cognitive impairment was prevalent in 20.7% of those with an Agatston score = 0, in 27.3% of those with a score greater than 0 and up to100, in 36.4% of those with a score greater than 100 and up to 300, and in 72.7% of those with a score > 300 (*p* trend = 0.004). In multivariable logistic regression with baseline CAC and high ABI in the model (Table 2), a dose-gradient association was observed for CAC associated with later cognitive impairment. Compared to Agatston score = 0, OR (95%CI) of 0 < −100, 100 < −300 and > 300 were 1.4 (0.6, 3.6), 2.3 (0.6, 9.7), and 7.9 (1.6, 38.5), respectively (final model, after backward elimination). CAC volume showed a similar association with cognitive impairment as that in Agatston scores (Supplementary Table 2). In addition to baseline CAC, high ABI (OR [95%CI]: 6.0 [1.5, 24.3]), fewer years of education, and having CAD were also significantly associated with worse cognition after backward elimination. When evaluating high ABI (Supplementary Table 3) and CAC (Supplementary Table 4) separately, both of these subclinical cardiovascular markers were independently and significantly associated with clinically relevant cognitive impairment.

Compared to the base model (comprised of year of education and existing CAD, covariates that were retained after backward selections), the addition of CAC Agatston scores and high ABI significantly improved the fit of the model, respectively (Table 3). The addition of CAC Agatston scores to the model including high ABI did also lead to a significant improvement in model fit. The results were consistent with CAC volume (data not shown).

In the subgroup of 116 participants having repeated CAC measures (Table 4), the backward selection model allowing for the full set of covariates, retained annual progression of CAC, but not baseline CAC. A

Table 3
Likelihood ratio tests for model fit evaluation.

Model	-2Log likelihood	*p* value
Base[a]	160.474	–
Base[a] + high ABI	152.694	0.005 (*vs.* Base)
Base[a] + CAC Agatston	151.945	0.003 (*vs.* Base)
Base[a] + CAC Agatston + high ABI	144.908	< 0.001 (*vs.* Base) 0.005 (*vs.* Base + high ABI) 0.008 (*vs.* Base + CAC Agatston)

CAC: coronary artery calcification, CAD: coronary artery disease.
[a] Base model was adjusted for year of education and existing CAD.

Table 4
Associations between annual CAC progression and clinically relevant cognitive impairment in participants with repeated CAC measures.

Events = 32/N = 116		Model 1		Model 2 (backward selection[b], final model)	
		OR (95%CI)[a]	*p* value	OR (95%CI)[a]	*p* value
Volume					
CAC progression		2.1 (1.1, 3.8)	0.019	1.7 (1.1, 2.9)	0.032
Baseline	0	ref			
CAC	0 < −100	0.5 (0.2, 1.9)	0.108		
	100 < −300	1.5 (0.2, 7.1)	0.661		
	> 300	2.2 (0.3, 13.4)	0.335		
Year of education		0.7 (0.5,1.1)	0.138	0.7 (0.4, 1.1)	0.094
High ABI		NA		5.7 (1.3, 24.3)	0.020
Diabetes duration		NA		1.7 (0.98, 2.8)	0.061
Agatston scores					
CAC progression		1.9 (1.1, 3.2)	0.021	1.5 (1.02, 2.4)	0.039
Baseline	0	ref			
CAC	0 < -100	0.5 (0.1, 1.8)	0.092		
	100 < -300	1.4 (0.3, 6.7)	0.672		
	> 300	2.0 (0.3, 12.8)	0.339		
Year of education		0.7 (0.5,1.1)	0.128	0.7 (0.4, 1.1)	0.088
High ABI		NA		5.8 (1.4, 24.7)	0.018
Diabetes duration		NA		1.6 (0.96, 2.8)	0.068

ABI: ankle-brachial index, BMI: body mass index, CAC: coronary artery calcium, CAD: coronary artery disease, CI: confidence interval, HbA1c: hemoglobin A1c, NA: not available, OR: odds ratio, SD: standard deviation.
Model 1: comprise baseline CAC, CAC progression, and year of education.
Model 2: Backward selection with a removal criterion of p value ≥ 0.10. In addition to baseline and progression of CAC, the high ABI, year of education, sex, age at cognitive tests, diabetes duration, apolipoprotein E4 status, ever smoking, BMI, HbA1c, cholesterols (high density lipoprotein and non-high density lipoprotein), triglycerides, urinary albumin excretion rate, hypertension, proliferative retinopathy, distal symmetric polyneuropathy, and statin use were offered for model selection.
[a] Per SD higher value for continuous variables.
[b] CAC progression, high ABI, year of education and diabetes duration were retained in the final model after backward selection.

Table 5
Association between CAC density and clinically relevant cognitive impairment after controlling for CAC volume in participants with baseline CAC over zero.

Events = 24/N = 68	Model 1		Model 2 (backward selection[b], final model)	
	OR (95%CI)[a]	*p* value	OR (95%CI)[a]	*p* value
Log (CAC volume)	2.6 (1.3, 5.4)	0.010	2.9 (1.3, 6.4)	0.008
CAC density	0.4 (0.1, 1.5)	0.161	0.3 (0.1, 1.2)	0.078
Year of education	0.5 (0.3,0.9)	0.018	0.4 (0.2, 0.8)	0.007
High ABI	NA		36.6 (2.1, 644.0)	0.014

ABI: ankle-brachial index, BMI: body mass index, CAC: coronary artery calcium, CAD: coronary artery disease, CI: confidence interval, HbA1c: hemoglobin A1c, NA: not available, OR: odds ratio, SD: standard deviation.
Model 1: comprise CAC volume, CAC density, and year of education.
Model 2: Backward selection with a removal criterion of $p \geq 0.10$. In addition to CAC volume and CAC density, the high ABI, year of education, sex, age at cognitive tests, diabetes duration, apolipoprotein E4 status, ever smoking, BMI, HbA1c, cholesterols (high density lipoprotein and non-high density lipoprotein), triglycerides, urinary albumin excretion rate, hypertension, proliferative retinopathy, distal symmetric polyneuropathy, and statin use were offered for model selection.
[a] Per SD higher value for continuous variables.
[b] Baseline CAC volume, CAC density, year of education, and high ABI were retained in the model after backward selection.

positive and significant association was found between CAC progression in volume (OR (95%CI) = 1.7 (1.1, 2.9), p value = 0.032) and later clinically relevant cognitive impairment. Besides CAC progression, years of education, diabetes duration, and high ABI were also retained in the final model. A similar association was observed for CAC progression in Agatston scores.

Table 5 displays the association of CAC density with cognitive impairment with controlling for CAC volume in participants with CAC over zero. After backward selection of the full set of covariates, both baseline CAC volume and CAC density were retained in the model, along with years of education and high ABI. The CAC density was marginally inversely associated with prevalent cognitive impairment at follow-up (OR [95 CI%]: 0.3 [0.1, 1.2], p value = 0.078).

No evidence was observed for interaction effect of sex on the associations between CAC measures and cognitive impairment in these data (all the interaction terms of sex with CAC measures were non-significant). When we additionally adjusted for sex and/or diabetes duration (if not retained after the backward elimination) in the final models, the results were consistent and there was an inferior model fit based on AIC (data not shown).

4. Discussion

In a prospective cohort of individuals living with type 1 diabetes since childhood, we found a significantly increased rate of later clinically relevant cognitive impairment among those with a greater burden of baseline CAC. CAC progression appeared a stronger risk factor for later cognitive impairment than initial CAC in this group of participants. An inverse association was also observed, in those with a CAC above zero, between CAC density and impaired cognition when controlling for CAC volume. These associations were independent of years of education, high ABI, and other risk factors that significantly contributed to the prediction models. While a previous report from the Pittsburgh EDC cohort found that a high ABI (> 1.3) quadrupled the risk of cognitive impairment [2], the present study extends this prior work by showing that calcified atherosclerotic plaque burden in the heart provides additional information over peripheral arterial disease in predicting impaired cognition in these middle-aged adults with type 1 diabetes.

There were 46% of type 1 diabetes individuals with prevalent CAC at a mean age of 37 years in this cohort, which is tripled compared to the CAC prevalence rate in the general population with similar age [35]. Over a mean interval of 5.5 years between two CAC scans, the incidence of CAC progression was 41% when defining progression with

the method by Hokanson et al. [25] (a square root transformed difference > 2.5). In those with baseline CAC = 0, 39% developed somewhat calcification over 5 years, a four-fold increase than that in the general population with a comparable age and a similar time interval between the two CAC scans [36].

There has been increasing interest regarding the role of cardiovascular disease and associated risk factors in age-related cognitive decline and dementia. CAC is an accurate index of subclinical atherosclerosis and the association with poor cognition function has consistently been observed in the general population across middle-to older -aged adults. Both the Cardiovascular Health Study (CHS) Cognition Study, with a population aged 80 + years [11], and the AGES-Reykjavik Study, a general population-based cohort with a mean age of 76 years [37], suggest an increased risk of dementia was associated with a greater burden of CAC in elderly populations. The Coronary Artery Risk Development in Young Adults (CARDIA) study further reported an association between poor cognition and a higher CAC in a middle-aged general population (mean age = 50 years) [12].

It is well recognized that atherosclerosis affects those with diabetes at a higher rate than occurs in the general population [38]. More recently, studies have identified worse cognitive performance in people with diabetes than in age-matched controls without diabetes [2,13]. However, very few studies have evaluated the predictive values of subclinical atherosclerosis on the cognitive complications of diabetes [13]. One study by Hugenschmidt et al. observed a modest association of baseline CAC with poorer performance on cognitive functioning tests in a group of older adults with type 2 diabetes, with average age of 67 years [13]. The current results are thus consistent with the prior work in an aging general population and in older adults with type 2 diabetes. Our work extends this to a middle-aged cohort of adults with childhood-onset type 1 diabetes (mean age: 37 years).

In addition, we observed a stronger magnitude of the effect of CAC progression over initial CAC, in the association with impaired cognition, emphasizing a dynamic nature for the influence of subclinical arthrosclerosis on the pathogenesis of cognitive impairment. Though previous studies has shown the predictive value of CAC progression in cardiovascular disease [24] and mortality [39], very few have studied the relation between dynamic changes in CAC and cognition functioning, to our best knowledge. The pathological pathways between vascular calcification and cognition function are not completely clear. Accelerated vascular calcification may contribute to white matter hyperintensities [40], reflecting cerebral small vessel disease [41], which are correlated to cognitive impairment and progression of amyloid burden [40,42]. Future studies are needed to determine whether a low extent of vascular calcification and/or a slower progression of CAC might reduce the development of diabetes-related cognitive impairment in adults with type 1 diabetes, and whether these findings apply to those with type 2 diabetes or to the general aging population as well.

Vascular calcification is an active and regulated process of calcium mineral deposition within arterial intimal and/or medial walls [43]. Unfortunately, conventional non-invasive CT scans cannot distinguish intimal and medial calcification. Existing evidence have shown that CAC primarily represents intimal calcification of focal plaque and atheromatous burden in the coronary arteries [14]. Though CAC may also reflect medial calcification, the degree of medial wall calcification in coronary arteries is difficult to determine and has not been clearly demonstrated to our knowledge. While, the association between high ABI and medial wall calcification has been well described [15].

Being distinct from previous studies, we included both CAC and high ABI in the prediction models. We found that the addition of high ABI to a model already included CAC led to a significant improvement in model fit. The addition of ABI could be explained by a higher plaque burden, involving not only the heart but the peripheral vessels as well. Importantly, however, our results also showed the independent associations of CAC and high ABI with clinically relevant cognitive impairment. We thus believe it is biologically plausible to postulate that CAC, mainly representing intimal calcification, and high ABI, mainly representing medial wall calcification, may respectively contribute to cognitive dysfunction, via distinct vascular pathological pathways, in people with type 1 diabetes. Indeed, animal and human studies have suggested that intimal and medial calcification, referred to as atherosclerosis and arteriosclerosis, respectively, are distinct vascular diseases [44] and the risk factors predicting atherosclerotic burden were not necessarily associated with medial calcification [45]. As such, there may be unique opportunities to identify new therapies targeting medial calcification that ultimately decrease the risk of cognitive impairment and dementia beyond general atherosclerosis prediction.

CAC has been proposed as a measure of “biological age” for its incremental value of risk prediction in addition to chronological age [46]. The present findings support that ABI may also be a useful aging index in addition to CAC for estimating “biological age”, especially for “vascular age”, at least in type 1 diabetes populations.

Our findings also suggest that routine monitoring of CAC and ABI may identify those type 1 diabetes individuals at an increased risk of cognitive impairment, facilitating an earlier implementation of appropriate evaluation and intervention to improve long-term prognosis.

One of our novel findings was that CAC density appears to be borderline protective against impaired cognition when controlling for CAC volume. Criqui et al. also reported an inverse association between CAC density and CVD events in the general population using MESA data [23]. A higher density of calcification might prompt more stable plagues, leading to a lower risk of incident acute coronary artery syndrome [23]. Thomas et al. subsequently identified inverse associations of many CVD risk factors with CAC density, including total cholesterol, blood pressure, smoking, diabetes, BMI, and a series of inflammation biomarkers (interleukin-6, C reactive protein, and Fibrinogen) [47]. To some extent, the factors above are directly or indirectly related to inflammation. As such, a lower degree of inflammation with higher CAC density may also explain the inverse relationship of CAC density and cognitive impairment, consistent with recently reported associations between increased inflammation and cognitive dysfunction and dementia [48,49].

Strengths of this study include the concurrent availability of ABI, CAC, and later neurocognitive evaluations in a well-characterized cohort of individuals with childhood-onset type 1 diabetes. The repeated measurement of CAC allows an assessment of the role of longitudinal change in CAC on cognition. An important limitation of the study was a relatively small sample size, which restricted stratified analysis or testing potential interactions, such as ABI and CAC. Another major consideration is that neurocognitive tests was not conducted at the time of first CAC was measured (the baseline of the present study), which limits the ability to determine causality. However, only one cognitively impaired participant in this analysis was diagnosed less than age 37 years (mean baseline age of the study). It is therefore likely that most of the cognitive impairment cases were truly incident during the follow-up period. Moreover, whether the present findings of vascular calcification with worse cognitive performance will extend to dementia outcome in older age remains unknown.

4.1. Conclusions

A greater burden of CAC is associated with higher odds of having clinically relevant cognitive impairment in middle-aged individuals with long-lasting type 1 diabetes. CAC progression was more informative than initial CAC in predicting impaired cognition. This implies a persistent and accumulating influence of subclinical atherosclerosis on diabetes-related cognition impairment. CAC and high ABI were independently associated with impaired cognition in this study, suggesting that the screening of CAC and ABI may allow early identification of type 1 diabetes patients at an increased risk of developing cognitive impairment.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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Contribution statement

J.G. conceived and designed the study, acquired, analyzed, and interpreted the data, drafted the manuscript, and performed the statistical analysis. K.A.N. conceived and designed the study, acquired and interpreted the data, edited and critically reviewed the manuscript for important intellectual content. T.C, R.G.M, C.R., and D.E. acquired and interpreted the data, edited and critically reviewed the manuscript for important intellectual content. T.J.O. conceived and designed the study, acquired and interpreted the data, edited and critically reviewed the manuscript for important intellectual content, and provided administrative and material support. T.J.O. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2018.11.003.

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