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Undiagnosed coronary artery disease in long-term type 1 diabetes. The Dialong study

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ABSTRACT

Aims: We studied the total prevalence of obstructive coronary artery disease (CAD), undiagnosed CAD and absent CAD in persons with ≥45-year duration of type 1 diabetes (T1D) versus controls, and associations with mean HbA_{1c}, LDL-cholesterol and blood pressure over 2–3 decades.
Methods: We included 76% ($n = 103$) of all persons with T1D diagnosed ≤1970 attending a diabetes center and 63 controls without diabetes. We collected 20–30 years of HbA_{1c}, LDL-cholesterol and blood pressure measurements. Participants without previously diagnosed coronary heart disease (CHD) underwent Computed Tomography Coronary Angiography (CTCA). Undiagnosed obstructive CAD was defined as any coronary stenosis >50% on CTCA, absent CAD as no detected plaque, and total obstructive CAD as either obstructive CAD on CTCA or previous CHD diagnosis.
Results: The prevalence of undiagnosed, absent and obstructive CAD was 24% (21/88), 16% (14/88) and 35% (36/103) in T1D versus 10% (6/60), 50% (30/60) and 14% (9/63) in controls (all $p < 0.05$). Mean HbA_{1c} was associated with undiagnosed obstructive CAD (OR 2.30 95% C.I. 1.13–4.69), while mean LDL-cholesterol was inversely associated with absent CAD (0.12, 0.04–0.43).
Conclusions: The prevalence of undiagnosed obstructive CAD was high (24%) in this cohort of long-term survivors with T1D. Mean LDL-cholesterol and HbA_{1c} were associated with CAD.

1. Introduction

Coronary heart disease (CHD) is an important cause of morbidity and mortality in persons with type 1 diabetes mellitus (T1D) with hazard ratios of acute coronary events far exceeding subjects without diabetes.[1–5] Persons with diabetes may be asymptomatic or exhibit atypical symptoms making it difficult to identify these people prior to a cardiac event.[6–8] First-line stress tests have a limited sensitivity in persons with diabetes.[9] Computed Tomography Coronary Angiography (CTCA) is a non-invasive technique that detects the presence, extent and severity of coronary artery disease (CAD) with high sensitivity and has the advantage of visualizing the coronary plaques compared to conventional angiography.[10,11]

Persons with T1D live much longer today, resulting in an ageing group of people with T1D. There is a high prevalence of cardiovascular disease (CVD) in long-term T1D.[1,12] However, the prevalence of undiagnosed CAD in this group is not known. Previous CTCA studies on asymptomatic CAD in diabetes, either relate mostly to persons with type 2 diabetes mellitus (T2D), do not focus on long-term T1D, or lack a control group.[13,14] The pathophysiology, age of diagnosis, lipid profile and the features of coronary atherosclerosis differ between T1D and T2D.[7,15,16] Therefore, it is essential to study CAD in persons with T1D rather than extrapolating data from studies on T2D, to guide clinical decision making.

Identifying predictors of undiagnosed CAD may help clinicians select when to investigate asymptomatic persons with long-term diabetes. Increased levels of mean HbA_{1c}, mean systolic blood pressure (SBP) and mean lipid levels have been associated with CVD events after 27 years of follow-up.[12,17] Although low-density lipoprotein-cholesterol (LDL-c) is a known risk factor for CHD in T1D, the guidelines on statin treatment is mainly based on data in T2D.[15,18] The association of time-

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dependent risk factors and undiagnosed CAD in long-term T1D has not been described previously.

With the aid of CTCA we aimed to find the prevalence of (i) undiagnosed obstructive CAD, (ii) absent CAD and (iii) total prevalence of obstructive CAD in persons with long-term T1D compared to controls, and (iv) identify the associations of the above with clinical findings and traditional risk factors, particularly mean HbA_{1c}, LDL-c and SBP levels collected over 20–30 years.

2. Subjects, materials and methods

2.1. Study design and participants

The Dialong study was a cross-sectional controlled study on long-term survivors of T1D conducted in 2015. The inclusion criteria have been described previously.[19] Briefly, we invited all patients with T1D diagnosed ≤1970 attending a state-funded T1D clinic; the Norwegian Diabetics' Centre (NDC) in Oslo, Norway. Out of 136 eligible people, 105 joined the main study. The control group ($n = 75$) without diabetes consisted of spouses/friends of the participants with diabetes. First degree relatives were excluded. As all the participants with diabetes were recruited from one single center, we had lab results and clinical data available from the previous decades. The regional ethics committee approved the study (project no. 2014/851), and the study conformed to the Declaration of Helsinki. All participants signed an informed consent.

2.2. Procedure

Background data were collected from patient charts at NDC and a clinical evaluation during the first visit. The participants attended Oslo University Hospital Ulleval (OUHU) for fasting blood tests, urine analysis and retinal photos.[19] All participants with diabetes without known CHD were referred to CTCA within a few months. Exclusion criteria were eGFR <45 or a fast irregular heart rate. As the CT radiation dose used on the diabetes group was low (median 1.6 mSv), the ethics committee approved that the control group also underwent the CTCA. All CT scans were analyzed by an experienced radiology consultant, and the reports were reviewed by a cardiologist for consideration of optimal medical treatment (OMT) or referral to invasive coronary angiography for possible revascularization procedures. Only participants with a suspicion of clinically significant disease were referred to invasive coronary angiography. If this procedure confirmed an intraluminal plaque resulting in >50% stenosis in a vessel supplying >10% of the myocardium,[20] the patient was offered percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) as per hospital protocol at OUHU.

2.3. CTCA

CTCA was performed on a Dual Source CT scanner (Somatom Definition Flash, Siemens, Erlangen, Germany). Metoprolol (5–20 mg) was administered to the participants prior to the CTCA to reduce the heart rate. At heart rates ≤65 beats/min a high-pitch scan was performed (128 × 0.6 mm collimation; 280 ms rotation time; pitch of 3.4; tube voltage of 100–120 kV) using prospective ECG-gating. A sequential scan-method was chosen for heart rates of 65–80 beats/min (prospectively ECG-gated), while heart rates >80 beats/min required a helical scan with retrospective ECG-gating. Nitroglycerin 0.4 mg was administered sublingually 1–3 min prior to scan for coronary artery expansion. Omnipaque™ 350 mg/mL (GE Healthcare, Princeton, New Jersey) was used for contrast enhancement. Image analysis was performed in SyngoVia® (Siemens Healthcare, Erlangen, Germany) by two independent readers.[21] The plaques were manually identified on cross-sectional and curved multi-planar images. The stenoses were measured manually and disagreements were solved by consensus.

2.4. Outcomes

Undiagnosed obstructive CAD was defined as the presence of a stenosis resulting in >50% lumen reduction in at least one of the coronary arteries on CTCA. *Absent CAD* was defined as no detected plaque in any of the coronary arteries on CTCA. *Previous CHD* was defined as either a previous episode of acute coronary syndrome, angina pectoris diagnosed by a cardiologist, or a previous revascularization procedure. *Total obstructive CAD* was defined as either previous CHD or obstructive CAD on CTCA. *Clinically significant CAD* was defined as the presence of a stenosis requiring revascularization therapy (PCI or CABG) during the study.

2.5. Variables

Many of the variables collected have been defined previously.[19] We analyzed the following lab tests in the Department of Medical Biochemistry OUHU: N-terminal pro-B-type natriuretic peptide (NT-proBNP), troponin-T, total cholesterol, HDL-c, LDL-c, triglycerides (Cobas 8000, c702, Roche Diagnostics, Germany, variation coefficient < 5%), and HbA_{1c} (current HbA_{1c}).[19]

All participants were asked by a medical doctor whether they had experienced episodes of retrosternal chest pain without a definitive non-cardiac cause, and if so whether it (i) was brought on by exercise, (ii) radiated to the jaw/left arm, or (iii) was relieved by rest/sublingual nitrogen within 10 min. Answering yes to at least two follow-up questions was defined as typical angina, otherwise as atypical chest pain or no pain. Shortness of breath was defined as NYHA stage ≥2. All participants had a 12-lead ECG, and an ischemic ECG was defined as either (i) pathological Q waves in two consecutive limb/chest leads, (ii) left bundle branch block, or (iii) poor R-wave progression in leads v1–v3.

2.6. Mean time-weighted variables - HbA_{1c}, LDL-c and SBP

Longitudinal HbA_1/HbA_{1c} values were available 1980–2015 and the calculation of mean HbA_{1c} ("Estimated Full Duration HbA_{1c}") has been described previously.[19] In the present study, we also created two additional mean HbA_{1c} variables for all participants that underwent CTCA and had available HbA_{1c} measurements prior to 1993 ($n = 74$). <93HbA1c was the mean time-weighted HbA_{1c} from the first value up until 1993 for each patient, and similarly >05HbA1c included all measurements from 2005 up until 2015.

LDL-c values were available 1983–2015, either as calculated by the Friedewald equation or as direct measurements.[22] A mean of 11 readings (SD = 4.1) were available per subject for a mean of 19 years (SD = 6.6). Mean LDL-c was calculated in several steps: First, we found the mean LDL-c per year with available readings. Then we identified the gaps of years without available readings, and applied the previous available year's value to the respective gaps. This was repeated until 2015 and finally the mean was calculated from all the years from the first available measurement in each individual. Yearly SBP readings were available 1969–2015. A mean of 19 readings (SD = 6.8) were available for a mean of 28 years (SD = 8.7). Mean SBP was calculated similarly to mean LDL-c.

2.7. Statistical analysis

The Dialong study was initially powered to study the association of CAD with skin advanced glycation end-products, hence no formal power analysis was performed regarding the prevalence of CAD in persons with T1D versus controls. Clinical characteristics were compared between the groups using two-tailed Student's *t*-test or Mann-Whitney *U* test for continuous and χ^2 for categorical data. We used Pearson's χ^2 to compare the prevalence of CAD between the groups and logistic regression analyses to adjust for any confounders. We intended to study the total effect of having T1D for ≥45 years on the

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development of CAD. Hence, we did not control for certain differences between the groups deemed to be a result of having long-term diabetes and a result of having different targets for primary prevention of CHD.

We did case-control sub-analyses only on the diabetes group using logistic regression analyses to study the effect of mean HbA_{1c}, mean LDL-c and mean SBP on the presence or absence of CAD. There were no missing data apart from one person each in the diabetes and control groups lacking current HbA1c, current LDL-c, troponin-t and NT-proBNP results and they were excluded from the relevant analyses. The significance level was set at $p < 0.05$. All analyses were performed using SPSS version 25 (IBM SPSS Inc., Armonk, NY: IBM Corp.).

3. Results

3.1. Characteristics of the participants

Out of 105 participants with T1D, 15 had previous CHD. Eighty-eight participants completed the CTCA, and a total of 103 either had a past history of CHD or completed the CTCA. In the control group, three had known CHD and 60 completed the CTCA (Fig. 1).

Clinical characteristics are presented in Table 1 for the CTCA population (full study population in Supplemental Table 1). There were no significant differences between the diabetes and control groups regarding the traditional risk factors; age, sex, BMI, smoking or family history of premature CHD. The diabetes group had a higher SBP and lower DBP than the control group. They also more frequently used statins, ACE-inhibitors/Angiotensin-receptor blockers (ACE-i/ARB) and aspirin and had lower fasting lipid levels.

Of the participants without previous CHD, 18 in the diabetes group and 8 in the control group described chest pain prior to being referred to CTCA ($p = 0.26$), with two and zero classified as typical angina in the diabetes and control groups respectively (Table 1). The median duration of diabetes was 48 (inter-quartile range 7) years and average mean HbA_{1c} was 8.0 ± 0.8% (63.5 ± 8.6 mmol/mol). Mean current HbA_{1c} of 7.4 ± 0.8% (57.8 ± 8.6 mmol/mol) in the long-term diabetes group was similar to the national mean HbA_{1c} as described previously.[19]

3.2. Prevalence of CAD

The diabetes group had a higher rate of undiagnosed obstructive CAD than the controls, with 24% (21/88) having >50% stenosis on CTCA versus 10% (6/60) of the controls, odds ratio (OR) 2.8 (95% CI 1.06–7.5), $p = 0.03$ (Fig. 2). The prevalence of total obstructive CAD (including previous CHD) was 35% (36/103) in the diabetes group and 14% (9/63) in the control group, OR 3.22 (95% C.I. 1.43–7.27), $p = 0.004$. Sixteen percent (14/88) of the diabetes group had absent CAD on CTCA versus 50% (30/60) in the control group, OR 0.19 (0.09–0.41), $p < 0.001$. This equates to a total prevalence of absent CAD of 14% (14/103) in the diabetes group when we include the participants with previous CHD. The differences between the groups remained significant when adjusting for age, sex and education level.

As a result of the CTCA findings, 24 participants (27%) in the diabetes group were referred to invasive coronary angiography and a total of 11 participants had either PCI ($n = 9$) or CABG ($n = 2$) performed as per study and hospital protocols.[20] Two out of three participants referred in the control group had a PCI procedure. Thus, 11/88 (12.5%) in the diabetes group and 2/60 (3%) in the control group had clinically significant CAD, OR 4.1 (95% C.I. 0.88–19.4), $p = 0.053$.

3.3. Predictors of undiagnosed obstructive CAD in long-term T1D

Table 2 shows the characteristics of the diabetes participants with obstructive disease on CTCA versus the diabetes participants with normal arteries or non-obstructive disease. The participants with undiagnosed obstructive CAD had significantly higher mean LDL-c, current HbA_{1c}, mean HbA_{1c} and <93HbA_{1c} than the participants without obstructive CAD. There was no significant difference in >05HbA_{1c} levels between the groups. They also had higher mean SBP, more persistent albuminuria and more use of ACE-i/ARB, however these differences were not significant ($p < 0.1$). Thirty-three percent of the diabetes participants with obstructive disease on CTCA reported episodes of chest pain versus 16% in the non-obstructive group ($p = 0.09$). Similarly, 36% (4/11) of the participants with diabetes with clinically significant CAD reported episodes of chest pain versus 18% (14/77) in the group without clinically significant CAD ($p = 0.16$).

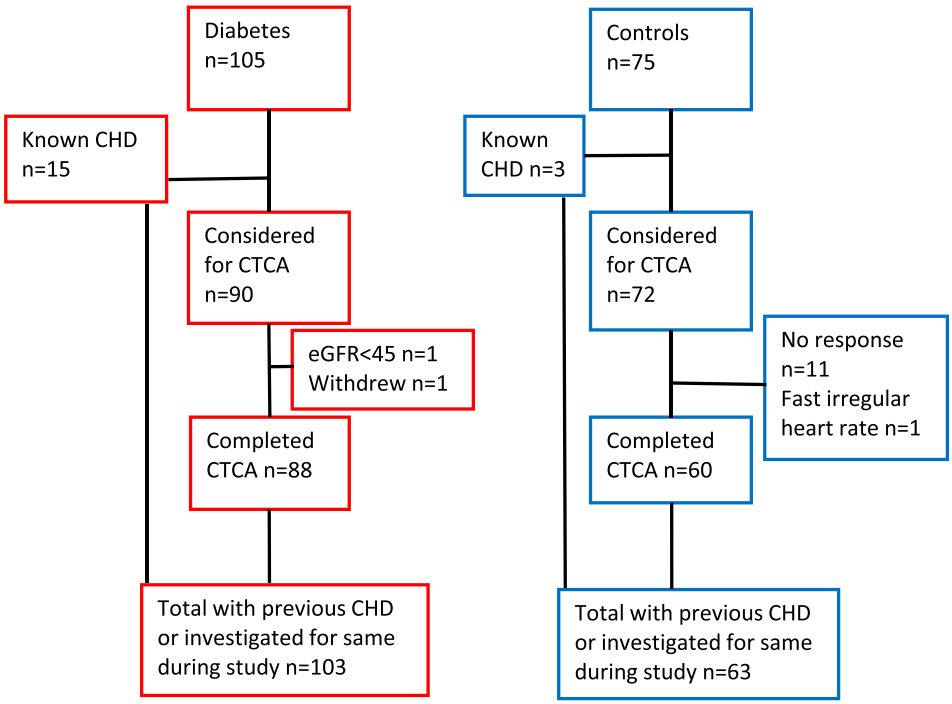

Fig. 1. Flowchart of participants.

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Table 1
Characteristics of the participants undergoing CTCA.

	Diabetes group ($n = 88$)	Control group ($n = 60$)	*P*
Demographics			
Age	61.5 ± 7.1	62.3 ± 6.8	0.46
Sex, male	41 (47)	26 (43)	0.70
College	53 (60)	49 (82)	**0.006**
Body mass index, kg/m^2	25.8 ± 3.9	25.5 ± 4.2	0.69
Smoker			
Daily	5 (5.7)	6 (10)	0.62
Ex-smoker	34 (39)	22 (37)	
Blood pressure			
Systolic, mm Hg	146 ± 20	137 ± 19	**0.006**
Diastolic, mm Hg	75 ± 8	82 ± 10	<**0.001**
Resting heart rate, beats per minute	68 ± 10	62 ± 9	<**0.001**
Diabetes related factors			
Current HbA_{1c}, %, mmol/mol	7.4 ± 0.8, 58 ± 8.6	5.4 ± 0.3, 36 ± 3.1	<**0.001**
Diabetes duration, years, median (IQR)	48 (7)		
Persistent albuminuria	14 (16)		
Retinopathy			
Background	49 (56)		
Proliferative	34 (39)		
Peripheral neuropathy	52 (59)	9 (15)	<**0.001**
Mean time-weighted variables			
Mean HbA_{1c} %, mmol/mol	7.9 ± 0.8, 63 ± 9		
<93HbA1c %, mmol/mol	8.0 ± 0.9, 64 ± 10		
>05HbA1c %, mmol/mol	7.7 ± 0.8, 61 ± 89		
Mean systolic blood pressure, mm Hg	130 ± 10.6		
Mean LDL-c, mmol/L	2.9 ± 0.6		
Cardiovascular disease			
Cerebrovascular disease	4 (5)	2 (3)	0.73
Peripheral vascular disease	3 (3)	0 (0)	0.15
Cardiovascular disease	6 (7)	2 (3)	0.36
Family history of premature coronary heart disease	10 (11)	6 (20)	0.10
Medication use			
Statins	39 (44)	5 (17)	<**0.001**
ACE-i/ARB	36 (41)	6 (20)	**0.002**
Aspirin	19 (22)	5 (17)	**0.03**
Symptoms/investigations			
Chest pain[a]	18 (20)	8 (13)	0.26
Shortness of breath	3 (3)	0 (0)	0.15
Ischemic ECG	10 (11)	1 (2)	**0.03**
Total cholesterol, mmol/L	5.1 ± 0.96	6.0 ± 1.01	<**0.001**
LDL-cholesterol, mmol/L	2.8 ± 0.83	3.9 ± 0.91	<**0.001**
HDL-cholesterol, mmol/L	2.1 ± 0.55	1.8 ± 0.52	<**0.001**
Triglycerides, mmol/L, median (IQR)	0.8 (0.4)	0.9 (0.5)	**0.004**
eGFR	85 ± 19	82 ± 13	0.18
Troponin-T, ng/L, median (IQR)	7 (5–12)	5 (3–7)	<**0.001**
NT-proBNP, ng/L	54 (30–140)	59 (35–82)	0.17

IQR, inter-quartile range; ACE-i/ARB, Angiotensin-Converting Enzyme-inhibitor or Angiotensin-receptor blocker; eGFR, Estimated glomerular filtration rate derived from the Modification of Diet in Renal Disease equation; NT-proBNP, N terminal-pro B-type natriuretic peptide. Significant *p*-values are outlined in bold.

[a] Chest pain, either typical angina or atypical chest pain. Data are mean ± SD or n (%) unless otherwise specified.

To determine which of the mean time-weighted variables were the most important predictors for (i) undiagnosed obstructive CAD and (ii) absent CAD on CTCA, logistic regression analyses were performed on the diabetes group. As <93HbA_{1c} and mean HbA_{1c} correlated highly with each other ($r = 0.92$, $p < 0.001$), only mean HbA_{1c} was included in the analyses. Fig. 3 shows the ORs for (i) undiagnosed obstructive CAD and (ii) absent CAD as outcomes. Mean HbA_{1c} was significantly associated with undiagnosed obstructive CAD, OR 2.30 (95% C.I. 1.13–4.69) while the associations with LDL-c, OR 1.88 (95% C.I. 0.75–4.68, $P = 0.18$) and SBP, $OR_{per\ 10mm\ Hb\ increase}$ 1.62 (95% C.I. 0.97–2.71 $P = 0.07$) did not reach statistical significance. Mean LDL-c had an inverse association with absent CAD, OR 0.12 (95% C.I. 0.036–0.43) while there were no associations with mean HbA_{1c} or mean SBP.

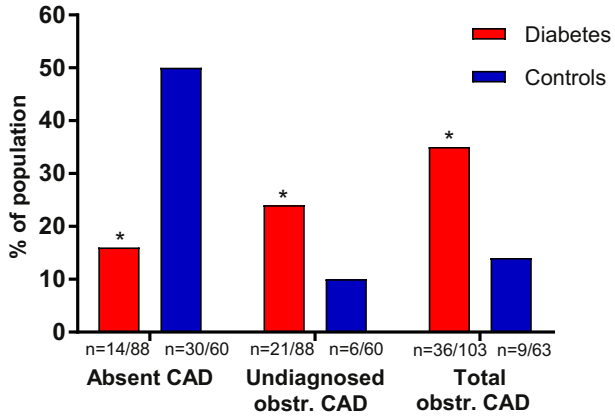

Fig. 2. Degree of coronary artery disease on CTCA. *p < 0.05 vs. controls. *Absent CAD* was defined as no detected plaque in any of the coronary arteries on CTCA. *Undiagnosed obstructive CAD* was defined as the presence of a stenosis resulting in >50% lumen reduction in at least one of the coronary arteries on CTCA. *Total obstructive CAD* was defined as either (i) previous CHD (previous acute coronary syndrome, verified angina pectoris, or a previous revascularization procedure) or (ii) obstructive CAD on CTCA.

4. Discussion

The main findings of the present study were that persons with long-term T1D without known CHD had a significantly higher prevalence of undiagnosed obstructive CAD than the controls (OR 2.8). Persons with long-term T1D were also three times less likely to have absent CAD on CTCA compared to controls, though 14% had normal coronary arteries. Higher mean HbA_{1c} was associated with undiagnosed obstructive CAD on CTCA and lower mean LDL-c was associated with absent CAD on CTCA.

The prevalence of undiagnosed obstructive CAD in our diabetic population compares to previous CTCA studies in diabetes.[23,24] However, these studies mainly included individuals with T2D and patients already referred to CTCA due to a clinical suspicion of CAD/other risk factors. In comparison, our cohort was not selected based on a clinical suspicion of CAD and as a group was relatively well controlled regarding other risk factors (mean LDL-c of 2.9, mean SBP of 130 and a smoking rate of 6%). The prevalence of obstructive CAD of 24% in this group is notably high. Other studies examining the prevalence of CHD in T1D have mainly used self-reported/documented episodes of CHD or ischemic ECG as outcomes, often presented as CVD, i.e. combined with cerebrovascular events and peripheral artery disease. Studies report that 40–44% of the participants with T1D with a duration of >50 years had a previous CVD event.[1,12] In the Diabetes Control and Complications Trial and follow-up study (DCCT/EDIC), 12–14% had any CVD event after 33 years of T1D.[2] This may partly be explained by a shorter duration of diabetes, strict inclusion criteria and stricter glycemic control as part of a clinical trial. In comparison, 20.4% of our survival cohort had a previous CVD event.

In the present study, 14% of long-term survivors with T1D had no coronary atherosclerosis and consequently have an excellent prognosis[25] adding to the evidence that diabetes is not a universal CHD-equivalent regarding future risk of CHD. There was a strong association between absent CAD and mean LDL-c over 20 years. For every lower unit (mmol/L) of LDL-c, the odds of having normal coronary arteries was eight times higher. This is supported by recent studies which have shown further benefit of having a very low LDL-c for secondary prevention of CVD events in the general population.[26] Dyslipidemia is a risk factor for CVD events in persons with T1D, however the recommendation on lipid lowering in T1D to reduce CVD events are mostly

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Table 2
Diabetes group. Characteristics of participants with undiagnosed obstructive CAD versus participants without obstructive CAD on CTCA.

	Undiagnosed obstructive CAD (21/88)	Non-obstructive CAD or normal arteries (67/88)	*P*
Background characteristics			
Age	63.3 ± 7.4	60.9 ± 6.9	0.16
Sex, male	11 (52)	30 (45)	0.54
Diabetes duration, years, median (IQR)	51 (8)	48 (6)	0.26
Body mass index, kg/m^2	26.1 ± 4.9	25.6 ± 3.6	0.63
Daily smoker	2 (10)	3 (4)	0.38
Family history of premature coronary heart disease	2 (10)	8 (12)	0.57
Statin use	12 (57)	27 (40)	0.17
ACE-i/ARB use	12 (57)	24 (36)	0.08
Clinical evaluation			
Chest pain[a]	7 (33)	11 (16)	0.09
Ischemic ECG	4 (19.0)	6 (9.0)	0.20
Persistent albuminuria	6 (29)	8 (12)	0.07
Proliferative retinopathy	10 (48)	24 (36)	0.33
Peripheral neuropathy	14 (67)	38 (57)	0.42
Current and mean time-weighted variables			
Current HbA_{1c}, %, mmol/mol	7.7 ± 1.0, 61 ± 11	7.3 ± 0.7, 56 ± 8	**0.03**
Mean HbA_{1c} %, mmol/mol	8.3 ± 0.9, 67 ± 10	7.8 ± 0.8, 62 ± 9	**0.01**
<93HbA_{1c} %, mmol/mol[b]	8.4 ± 1.0, 68 ± 11	7.8 ± 0.9, 62 ± 10	**0.03**
>05HbA_{1c} %, mmol/mol[b]	7.8 ± 0.8, 62 ± 9	7.6 ± 0.8, 60 ± 9	0.31
Current systolic blood pressure mm Hg	150 ± 23	145 ± 19	0.35
Mean systolic blood pressure, mm Hg	133 ± 10.5	129 ± 10.5	0.10
Current LDL-cholesterol, mmol/L	2.8 ± 0.8	2.8 ± 0.8	0.97
Mean LDL-cholesterol, mmol/L	3.2 ± 0.6	2.8 ± 0.6	**0.03**

IQR, inter-quartile range; ACE-i/ARB, Angiotensin-Converting Enzyme-inhibitor or Angiotensin-receptor blocker.
Significant *p*-values are outlined in bold.
[a] Chest pain, either typical angina or atypical chest pain.
[b] Based on 74 participants with available data. Data are mean ± SD or n (%) unless otherwise specified.

based on extrapolation from studies on adults with T2D.[15,18] The lipid profile seen in T1D is more favorable, however the qualitative differences in LDL-c and HDL-c may be atherogenic.[18] The present study shows a very strong association between coronary atherosclerosis and mean LDL-c level over twenty years, however prospective studies are needed to establish an optimal LDL-c target in T1D.

The associations of several time-dependent risk factors and undiagnosed obstructive CAD in long-term T1D have to our knowledge not been studied previously. While there was a significant association between mean HbA_{1c} and undiagnosed obstructive CAD, we may have lacked power to detect a significant association between the latter and mean LDL-c and SBP (Fig. 3). Interestingly, while mean < 93HbA_{1c} was significantly higher in the group with undiagnosed obstructive CAD compared to the participants with no/non-obstructive CAD (8.4% versus 7.8%), the mean value from the previous 10 years (>05HbA_{1c}) was not. This is consistent with the findings from the DCCT/EDIC cohort where 6.5 years of intensive diabetes therapy had beneficial long-term effects on the incidence of CVD events up to 30 years later and argues for the role of metabolic memory, also in an older age group as in the present study.[2] The role of cumulative glycemia as a strong risk factor for cardiac events in persons with T1D was recently confirmed in the DCCT/EDIC study.[17] As there is a strong longitudinal correlation between HbA_{1c} levels and traditional CVD risk factors such as triglycerides and LDL-c levels in T1D,[27] our results emphasize the importance of good glycemic control and lower LDL-c over time to prevent CHD in these patients.

Our cohort of T1D participants was not entirely asymptomatic. Due to the structured questioning, the participants might have revealed symptoms of chest pain/discomfort that they had not reflected on and shared with their physicians. The rate of participants with diabetes reporting chest pain was twice as high in the group with undiagnosed obstructive CAD or clinically significant CAD versus those without. However, the difference was not significant. There is evidence suggesting that silent ischemia is more common in patients with cardiac autonomic neuropathy[28] not assessed in the present study. However, we found no association between peripheral neuropathy and obstructive CAD. Although our results would have to be confirmed in a larger study, they advocate asking persons with T1D about chest pain on their yearly follow-up.

Regarding treatment of stable CAD in diabetes, a previous randomized controlled trial (RCT) on persons with T2D only found a benefit on major CVD events on patients undergoing CABG versus OMT, and not for patients treated with PCI versus OMT. However, patients with left main stem disease were excluded and patients with proximal left anterior descending artery disease were generally treated with CABG.[29] CABG was superior to PCI in a trial comparing the two revascularization techniques for multi-vessel disease in diabetes (both T1D and T2D).[30] There are no similar trials focusing on T1D. The European Society of Cardiology recommends revascularization therapy to patients with stable CHD and the presence of an obstructive stenosis >50% of the lumen diameter in the left main stem or proximal left anterior descending artery and/or a fractional flow reserve ≤0.80 for improved prognosis (2.2).[20] Hence, in the present study, one out of eight in the diabetes group were treated with revascularization therapy combined with OMT to improve prognosis. RCTs looking at secondary preventive measures in non-obstructive CAD detected by CTCA are lacking, and decisions on OMT in our participants that did not qualify for revascularization, were on the discretion of the cardiologist or diabetes physician.

While CTCA has an excellent sensitivity for detecting coronary atherosclerotic plaques, the specificity for diagnosing obstructive CAD with 64-slice CTCA compared with invasive coronary angiography varied between 64% and 90%.[31–33] In the present study, we utilized 128-slice CTCA, however only 11 out of 24 participants (46%) in the diabetes group and 2 out of 3 in the control group (67%) that were referred to invasive coronary angiography had revascularization. While screening in unselected subjects with diabetes is not currently recommended,[34–36] it has been suggested that there may be a benefit in screening high-risk sub-groups with diabetes.[37] Modern CTCA is an excellent test to non-invasively identify the presence of atherosclerosis in the coronary arteries at a low radiation dose.[38] The presence of CAD on CTCA has been linked to cardiac events in persons with diabetes, and conversely the absence of CAD on CTCA with a low event rate.[24,25,39,40] The FACTOR 64 RCT, which was underpowered due to fewer events than anticipated, did not find a benefit of using CTCA to screen participants with a mean diabetes duration of 12 years for CAD.[41] The duration was short compared to our study, and further RCTs are needed to assess whether

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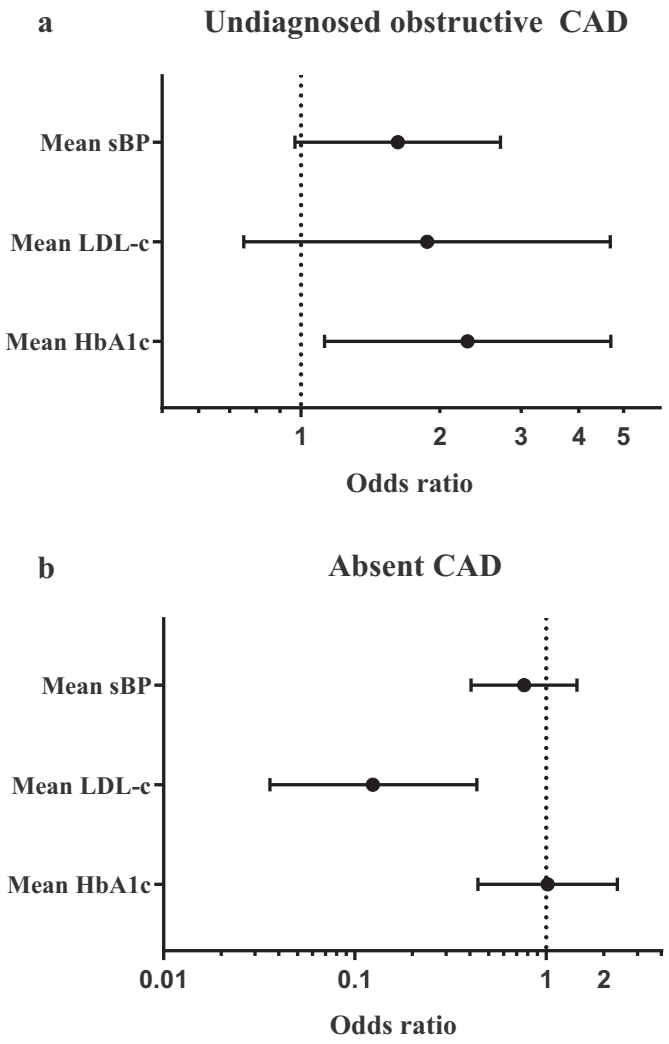

Fig. 3. Odds ratios and 95% C.I. for the associations of (i) mean SBP (per 10 mm Hg increase); (ii) mean LDL-c (per 1 mmol/L increase); and (iii) mean HbA_{1c} (per 1% increase) with panel a, undiagnosed obstructive CAD and panel b, absent CAD as outcomes in full models.

high-risk sub groups with diabetes, including persons with long-term T1D, may benefit from screening with CTCA.

There are several limitations to our study. The cross-sectional study design cannot give prognostic answers to the diagnosis of obstructive CAD and the utility of CTCA. Our study represents a survival cohort thus we do not present the total burden of CHD in long-term T1D. The control group were mainly spouses of the participants in the diabetes group, which could represent a selection bias as they had similar environmental exposures to the diabetes group with a resulting underestimation of the effect of having T1D. As patients with diabetes may have a different lifestyle to the general population, our choice of control group may not be a perfect representation of the general population. Additionally, the control group should ideally have been larger. However, the prevalence of past CHD events of 5% in the control group, compares to 7% of 60-year olds in a previous larger ($n = 4364$) Norwegian study ($p = 0.49$).[42] Further, our main objective was to have a control group which was free of the exposure we wanted to study, namely the presence of T1D, but otherwise similar in age, sex, and environmental factors. While our cohort of persons with T1D of an extreme duration is relatively large, we had limited number of cases in statistical terms, which may have resulted in type II errors when looking at predictors for CAD. Strengths of our study includes a high inclusion rate of our cohort of persons with T1D who are very well characterized with imaging of the coronary anatomy, and the availability of longitudinal HbA_{1c}, LDL-c and SBP readings for the past 20–30 years.

In conclusion, there was a high prevalence of undiagnosed obstructive CAD in this unselected cohort of persons with long-term T1D compared with controls. Yet, 14% had normal coronary arteries after 50 years of T1D. Worse long-term control of LDL-c was inversely associated with having absent CAD and mean HbA_{1c} was associated with undiagnosed obstructive CAD, confirming the importance of strict glucose and lipid control in T1D. The present study also adds to the argument of evaluating persons with long-term T1D with poor lipid and glycemic control for obstructive CAD with CTCA. Further prospective studies regarding screening for CAD and optimal lipid levels for prevention of CHD are needed for people with long-term T1D.

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Declarations of interest

None.

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