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.

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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

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 $8.0 \pm 0.8\%$ (63.5 ± 8.6 mmol/mol). Mean current HbA_{1c} of $7.4 \pm 0.8\%$ (57.8 ± 8.6 mmol/mol) in the long-term diabetes group was similar to the national mean HbA1c 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 ($p = 0.16$).
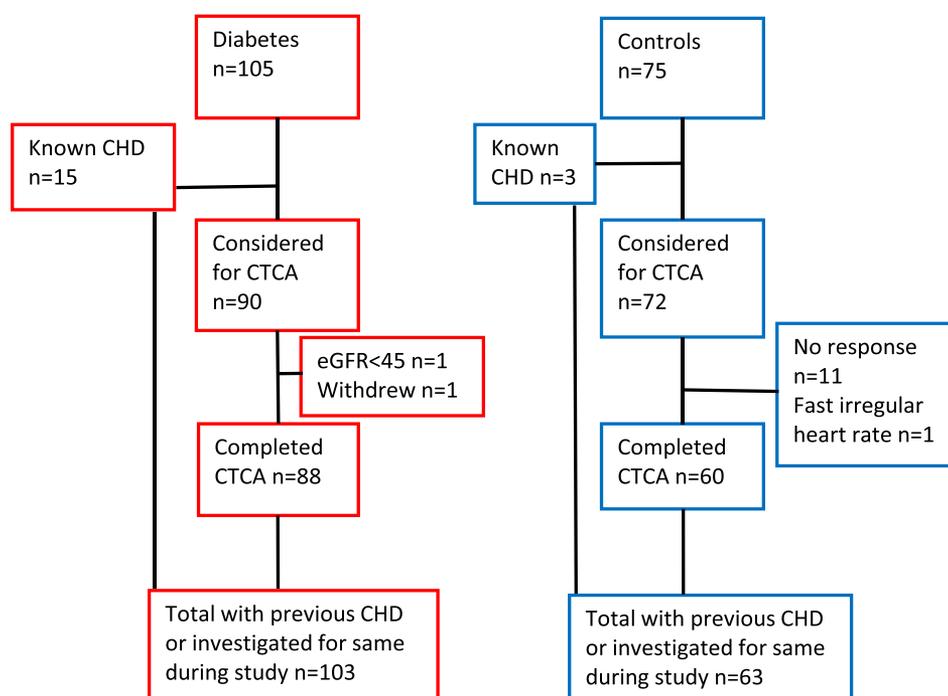

Fig. 1. Flowchart of participants.

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/m²	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 <93HbA1c 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 $P =$
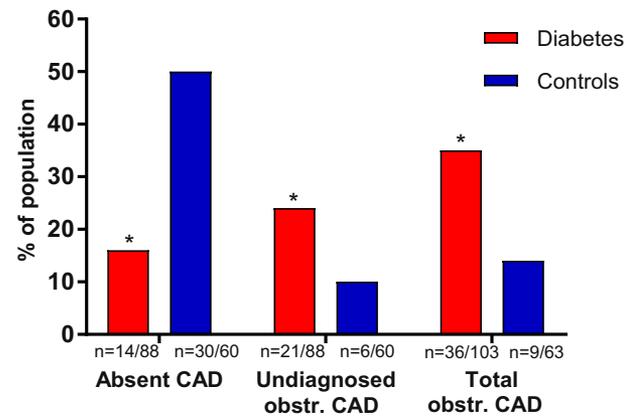

Fig. 2. Degree of coronary artery disease on CTCA. *p < 0.05 vs. controls. *Absent CAD* was defined as no detected plaque in any of the coronary arteries on CTCA. *Undiagnosed obstructive CAD* was defined as the presence of a stenosis resulting in >50% lumen reduction in at least one of the coronary 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.

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.

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

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/m²	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

a   Undiagnosed obstructive CAD
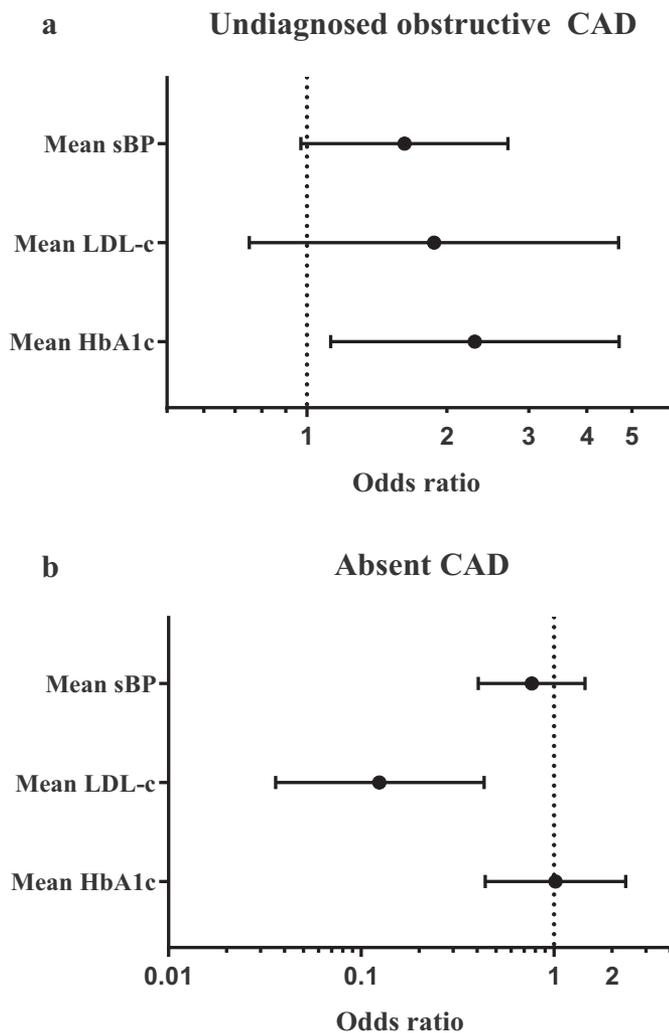

b   Absent CAD

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.

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.

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

References

1. Adamsson Eryd S, Svensson AM, Franzen S, Eliasson B, Nilsson PM, Gudbjornsdottir S. Risk of future microvascular and macrovascular disease in people with Type 1 diabetes of very long duration: a national study with 10-year follow-up. Diabet Med 2017;34:411-8.
2. DCCT/EDIC. Intensive diabetes treatment and cardiovascular outcomes in type 1 diabetes: the DCCT/EDIC study 30-year follow-up. Diabetes Care 2016;39:686-93. 2016/02/11 ed.
3. Soedamah-Muthu SS, Fuller JH, Mulnier HE, Raleigh VS, Lawrenson RA, Colhoun HM. High risk of cardiovascular disease in patients with type 1 diabetes in the U.K.: a cohort study using the general practice research database. Diabetes Care 2006;29:798-804.
4. Gagnum V, Stene LC, Jenssen TG, et al. Causes of death in childhood-onset Type 1 diabetes: long-term follow-up. Diabet Med 2017;34:56-63.
5. Livingstone SJ, Looker HC, Hothersall EJ, et al. Risk of cardiovascular disease and total mortality in adults with type 1 diabetes: Scottish registry linkage study. PLoS Med 2012;9:e1001321.
6. Jouven X, Lemaitre RN, Rea TD, Sotoodehnia N, Empana JP, Siscovick DS. Diabetes, glucose level, and risk of sudden cardiac death. Eur Heart J 2005;26:2142-7.
7. Retnakaran R, Zinman B. Type 1 diabetes, hyperglycaemia, and the heart. Lancet 2008;371:1790-9.
8. Larsen J, Brekke M, Sandvik L, Arnesen H, Hanssen KF, Dahl-Jorgensen K. Silent coronary atheromatosis in type 1 diabetic patients and its relation to long-term glycemic control. Diabetes 2002;51:2637-41.
9. Kamalesh M, Feigenbaum H, Sawada S. Assessing prognosis in patients with diabetes mellitus—the Achilles' heel of cardiac stress imaging tests? Am J Cardiol 2007;99:1016-9.
10. Kolossvary M, Szilveszter B, Edes IF, et al. Comparison of quantity of coronary atherosclerotic plaques detected by computed tomography versus angiography. Am J Cardiol 2016;117:1863-7.
11. Johnson TR, Nikolaou K, Busch S, et al. Diagnostic accuracy of dual-source computed tomography in the diagnosis of coronary artery disease. Investig Radiol 2007;42:684-91.
12. Tinsley LJ, Kupelian V, D'Eon SA, et al. Association of glycemic control with reduced risk for large-vessel disease after more than 50 years of type 1 diabetes. J Clin Endocrinol Metab 2017;102:3704-11.
13. Kim JJ, Hwang BH, Choi IJ, et al. Impact of diabetes duration on the extent and severity of coronary atheroma burden and long-term clinical outcome in asymptomatic type 2 diabetic patients: evaluation by coronary CT angiography. Eur Heart J Cardiovasc Imaging 2015;16:1065-73.

14. Byrne C, Jensen T, Hjortkjaer HO, et al. Myocardial perfusion at rest in patients with Diabetes Mellitus Type 1 compared with healthy controls assessed with Multi Detector Computed Tomography. Diabetes Res Clin Pract 2015;107:15-22.

15. de Ferranti SD, de Boer IH, Fonseca V, et al. Type 1 diabetes mellitus and cardiovascular disease: a scientific statement from the American Heart Association and American Diabetes Association. Diabetes Care 2014;37:2843-63.

16. Djaberi R, Schuijf JD, Boersma E, et al. Differences in atherosclerotic plaque burden and morphology between type 1 and 2 diabetes as assessed by multislice computed tomography. Diabetes Care 2009;32:1507-12.

17. DCCT/EDIC. Risk factors for cardiovascular disease in type 1 diabetes. Diabetes 2016;65:1370-9.

18. Ryden L, Grant PJ, Anker SD, et al. ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD - summary. Diab Vasc Dis Res 2014;11:133-73.

19. Holte KB, Juel NG, Brox JI, et al. Hand, shoulder and back stiffness in long-term type 1 diabetes; cross-sectional association with skin collagen advanced glycation end-products. The Dialong study. J Diabetes Complicat 2017;31:1408-14.

20. Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J 2014;35:2541-619.

21. Austen WG, Edwards JE, Frye RL, et al. A reporting system on patients evaluated for coronary artery disease. Report of the Ad Hoc Committee for Grading of Coronary Artery Disease, Council on Cardiovascular Surgery, American Heart Association. Circulation 1975;51:5-40.

22. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972;18:499-502.

23. Budoff MJ, Raggi P, Beller GA, et al. Noninvasive cardiovascular risk assessment of the asymptomatic diabetic patient: the Imaging Council of the American College of Cardiology. J Am Coll Cardiol Img 2016;9:176-92.

24. Min JK, Labounty TM, Gomez MJ, et al. Incremental prognostic value of coronary computed tomographic angiography over coronary artery calcium score for risk prediction of major adverse cardiac events in asymptomatic diabetic individuals. Atherosclerosis 2014;232:298-304.

25. Celeng C, Maurovich-Horvat P, Ghoshhajra BB, Merkely B, Leiner T, Takx RA. Prognostic value of coronary computed tomography angiography in patients with diabetes: a meta-analysis. Diabetes Care 2016;39:1274-80.

26. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017;376:1713-22.

27. DCCT/EDIC. Coprogression of cardiovascular risk factors in type 1 diabetes during 30 years of follow-up in the DCCT/EDIC study. Diabetes Care 2016;39:1621-30.

28. Vinik AI, Ziegler D. Diabetic cardiovascular autonomic neuropathy. Circulation 2007;115:387-97.

29. Frye RL, August P, Brooks MM, et al. A randomized trial of therapies for type 2 diabetes and coronary artery disease. N Engl J Med 2009;360:2503-15.

30. Farkouh ME, Domanski M, Sleeper LA, et al. Strategies for multivessel revascularization in patients with diabetes. N Engl J Med 2012;367:2375-84.

31. Budoff MJ, Dowe D, Jollis JG, et al. Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial. J Am Coll Cardiol 2008;52:1724-32.

32. Meijboom WB, Meijs MF, Schuijf JD, et al. Diagnostic accuracy of 64-slice computed tomography coronary angiography: a prospective, multicenter, multivendor study. J Am Coll Cardiol 2008;52:2135-44.

33. Miller JM, Rochitte CE, Dewey M, et al. Diagnostic performance of coronary angiography by 64-row CT. N Engl J Med 2008;359:2324-36.

34. Muhlestein JB, Moreno FL. Coronary computed tomography angiography for screening in patients with diabetes: can enhanced detection of subclinical coronary atherosclerosis improve outcome? Curr Atheroscler Rep 2016;18:64.

35. Perk J, De Backer G, Gohlke H, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Eur Heart J 2012;33:1635-701.

36. Wolk MJ, Bailey SR, Doherty JU, et al. ACCF/AHA/ASE/ASNC/HFSA/HRS/SCAI/SCCT/SCMR/STS 2013 multimodality appropriate use criteria for the detection and risk assessment of stable ischemic heart disease: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. J Am Coll Cardiol 2014;63:380-406.

37. Andreini D, Screening CT. Angiography in asymptomatic diabetes mellitus? J Am Coll Cardiol Img 2016;9:1301-3.

38. Stocker TJ, Deseive S, Leipsic J, et al. Reduction in radiation exposure in cardiovascular computed tomography imaging: results from the Prospective Multicenter Registry on RadiaTion Dose Estimates of Cardiac CT AngIOgraphy IN Daily Practice in 2017 (PROTECTION VI). Eur Heart J 2018;39:3715-23.

39. Kang SH, Park GM, Lee SW, et al. Long-term prognostic value of coronary CT angiography in asymptomatic type 2 diabetes mellitus. J Am Coll Cardiol Img 2016;9:1292-300.

40. Plank F, Friedrich G, Dichtl W, et al. The diagnostic and prognostic value of coronary CT angiography in asymptomatic high-risk patients: a cohort study. Open Heart 2014;1:e000096.

41. Muhlestein JB, Lappe DL, Lima JA, et al. Effect of screening for coronary artery disease using CT angiography on mortality and cardiac events in high-risk patients with diabetes: the FACTOR-64 randomized clinical trial. JAMA 2014;312:2234-43.

42. Graff-Iversen S, Jenum AK, Grotvedt L, Bakken B, Selmer RM, Sogaard AJ. Risk factors for myocardial infarction, stroke and diabetes in Norway. Tidsskr Nor Laegeforen 2007;127:2537-41.