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Changes in glycaemic control and risk of coronary artery disease in type 1 diabetes mellitus: findings from the Pittsburgh Epidemiology of Diabetes Complications Study (EDC)

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Abstract

Aims/hypothesis To complete a comparative analysis of studies that have examined the relationship between glycaemia and cardiovascular disease (CVD)/coronary artery disease (CAD) and perform a prospective analysis of the effect of change in glycosylated Hb level on CAD risk in the Pittsburgh Epidemiology of Diabetes Complications Study (EDC) of childhood-onset type 1 diabetes mellitus ($n=469$) over 16 years of two yearly follow-up. *Methods* Measured values for HbA_1 and HbA_{1c} from the EDC were converted to the DCCT-standard HbA_{1c} for change analyses and the change in HbA_{1c} was calculated (final HbA_{1c} minus baseline HbA_{1c}). CAD was defined as EDC-diagnosed angina, myocardial infarction, ischaemia, revascularisation or fatal CAD after medical record review. *Results* The comparative analysis suggested that glycaemia may have a stronger effect on CAD in patients without, than in those with, albuminuria. In EDC, the change in HbA_{1c} differed significantly between CAD cases ($+0.62\pm 1.8\%$) and non-cases ($-0.09\pm1.9\%$) and was an independent predictor of CAD. *Conclusions/interpretation* Discrepant study results regarding the relationship of glycaemia with CVD/CAD may, in part, be related to the prevalence of renal disease. Measures of HbA_{1c} change over time show a stronger association with CAD than baseline values.

Abbreviations

CAD	coronary artery disease
CVD	cardiovascular disease
EDIC	Epidemiology of Diabetes Interventions and Complications Trial
EDC	Epidemiology of Diabetes Complications Study
eGDR	estimated glucose disposal rate
WESDR	Wisconsin Epidemiologic Study of Diabetic Retinopathy

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Introduction

Cardiovascular disease (CVD) occurs with greater frequency in those with diabetes mellitus, a finding particularly striking in women [1]. These observations are especially true for those with type 1 diabetes mellitus, in whom coronary heart disease is increased tenfold or greater [2, 3]. However, while the role of glycaemia in the development of microvascular diabetes complications, such as retinopathy and albuminuria, is well established [4, 5], its role in CVD in patients with type 1 diabetes remains unclear. Indeed, epidemiological studies of glycaemia and coronary artery disease (CAD) in patients with type 1 diabetes have reported conflicting data. Although a study of older-onset

type 1 diabetes patients without renal disease showed a significant and independent association between HbA₁ and CAD events in men (but not women) after controlling for traditional cardiovascular risk factors [6], four prospective incident studies have not. The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) reported that, whereas the HbA_1 level was associated with mortality from any heart disease (not controlling for renal disease), there was no significant relationship with myocardial infarction or angina specifically [7]. A significant age- and duration-adjusted relationship reported in men (but not women) in the EURODIAB study disappeared with further adjustment for other cardiovascular risk factors [8]. A 10 year follow-up of patients at the Hvidore hospital in Denmark also failed to show an independent effect of HbA_{1c}, though the authors suggested that this might have been due to the small number of events [9]. Finally, in our Pittsburgh Epidemiology of Diabetes Complications Study (EDC) 10 year follow-up analysis, we found no significant relationship between either baseline glycaemia [10] or cumulative exposure [11] and CAD incidence. Overall, in a meta-analysis, Selvin et al. reported a nonsignificant odds ratio of 1.15 per 1% change in HbA_{1c} (95% CI 0.92–1.43) [12].

In contrast, a recent meta-analysis of clinical trials by Stettler et al. found that improved glycaemic control reduces the incidence of CAD and CVD in type 1 as well as type 2 diabetes, although the effect was less marked in type 2 diabetes [13]. A large portion of the type 1 population in the meta-analysis comprised the DCCT study population. The DCCT recently reported a major beneficial effect of intensive glycaemic control on cardiovascular outcomes in those who received intensive therapy for approximately 6 years, after 11 years of further follow-up [14]. These findings differ from those of the UK Prospective Diabetes Study (UKPDS) in type 2 diabetes, in which the benefit of intensive therapy was marginal after a mean of 10 years in-trial follow-up [15].

In order to explore possible reasons for these differences, we now compare in more detail the characteristics of these type 1 diabetes epidemiological cohorts and the participants in DCCT/Epidemiology of Diabetes Interventions and Complications Trial (EDIC). We also examine whether change in HbA_{1c} predicts CAD risk in EDC, even though baseline glycaemia does not, in an effort to reconcile differences between the epidemiological and clinical trial data in type 1 diabetes.

Methods

Comparative study selection

In the comparative analysis we included studies that: (1) prospectively examined cardiovascular outcomes of interest (angina, ischaemia, myocardial infarction, CAD death, revascularisation) in type 1 diabetes; (2) reported an HbA_{1c}/ HbA_1 measurement; and (3) compared major cardiovascular risk factor levels (e.g. blood pressure [BP], lipids and smoking) between incident CAD cases and non-cases.

Reported lipoprotein levels were converted to mmol/l and 24 h AER was converted to µg/min when necessary. One study stratified variables by sex [6]; therefore, values were recalculated to pool results for men and women. The CAD outcome in each study was myocardial infarction or death due to CAD. The EURODIAB study included angina when previously diagnosed by a physician, while in EDC it was diagnosed by a research physician; both also included a history of revascularisation. In DCCT/EDIC, 'cardiovascular' incidence included a history of revascularisation as well as cerebrovascular events ($n=6$).

Data from the WESDR and the Hvidore hospital studies [3, 4, 9] were not included in this analysis since baseline values for CAD cases and non-cases are not currently published.

Change analysis

Participants in EDC, a 16-year prospective study of risk factors for complications of type 1 diabetes, were selected. Participants were originally recruited from the Children's Hospital of Pittsburgh registry of individuals who had been diagnosed with childhood-onset (<17 years) type 1 diabetes between 1950 and 1980 at that hospital or seen there within 1 year of diagnosis.

Recruitment and study methods have been described previously [11, 16, 17]. Briefly, there were 658 participants in the baseline examination (1986–1988). Participants were seen in clinic at 2 year intervals for a 10-year period then follow-up continued with annual surveys ending, for this analysis, in 2002–2004. Those who refused to attend clinic were asked to complete a medical history questionnaire. Participants with no follow-up information ($n=3$) and prevalent CAD cases ($n=52$), were excluded from this incidence analysis. Follow-up data for the remaining 603 participants are shown in Table 1. Analyses of change included only participants with at least two HbA_{1c} values (from baseline to the cycle before CAD incidence or censoring; $n=469$).

Clinical evaluation and procedures

Participants completed questionnaires that include demographics and medical history and health behaviour information. Hospitalised events were confirmed by medical records and ECGs were Minnesota-coded by a trained observer. Standardised sitting BP was measured according to the Hypertension Detection and follow-up Program pro-

Table 1 Baseline characteristics of CAD and cardiovascular disease (DCCT) cases and non-cases in type 1 diabetes studies

	EDC CAD+	CAD−	DCCT/EDIC CVD+	CVD−	EURODIAB CAD+	CAD−	Lehto et al. CAD+	CAD−
n	139	464	83	1,358	151	2,178	28	149
Sex (% male)	55	49	48	53	46*	54	47	61
Age (years)	32.9±6.6***	25.5±7.2	31±6***	27±7	38.1±10.5***	31.7±9.5	57.7**,a	54.9
Disease duration (years)	24.8±6.8***	17.3±6.7	7±5*	6±4	19.0±10.3***	14.0±8.8	18.3***,b	13.4
Study follow-up (years)	16		16.5		7		7	
BMI (kg/m^2)	24.0±3.3	23.4±3.2	24.0±2.8*	23.3±2.8	23.9±2.9	23.5±2.8	25.1	25.3
Systolic BP (mmHg)	120.0± 18.1***	110.6±12.8	116±11	114±12	126.9±19.9***	119.7±16.5	NA	NA
Diastolic BP (mmHg)	77.0±12.6**	71.2±9.9	73±9	73±9	75.0±11.8	75.0±11.2	NA	NA
Hypertension (%)	38.1***	18.1	None	None	34***	21	28.6	37.6
Serum creatinine (μmol/l)	107.9± 97.2***	84.0±76.0	69.0±12.4	71.6±13.3	NA	NA	NA	NA
Total cholesterol (mmol/l)	5.37±1.15***	4.78±1.00	5.10±0.88***	4.53±0.86	5.55±1.20***	5.30±1.12	6.97	6.60
HDL-cholesterol (mmol/l)	1.31±0.32***	1.42±0.31	1.30±0.34	1.32±0.31	1.46±0.44	1.51±0.43	1.66	1.61
LDL-cholesterol (mmol/l)	3.85±3.14***	2.85±0.80	3.29±0.75***	2.82±0.75	3.52±1.09*	3.32±0.97	4.61	4.40
Triacylglycerol (mmol/l)	1.53 ± 1.10***	1.10±0.90	1.00±0.53*	0.91±0.54	1.06 (0.74– 1.53)*	0.90 (0.69– 1.25)	1.56	1.46
Glycohaemoglobin (%)^c	HbA$_1$ 10.4± 1.9	HbA$_1$ 10.4± 1.8	HbA$_{1c}$ 9.5± 1.8*	HbA$_{1c}$ 9.0± 1.6	GHb 6.85± 1.63	GHb 6.63± 1.88	GHbA 10.7*	GHbA$_1$ 9.8
Pulse (beats per min)	79.7±10.0	77.8±9.8	70±12	68±11	NA	NA	NA	NA
AER (μg/min)	581.4± 1,199.1***	153.1± 486.5	13.4±15.8*	10.9±12.9	20.2 (8.6– 87.9)***	10.7 (6.5– 21.9)	NA	NA
Nephropathy status (% ≥MA)	67***	38	8	5	50***	27	None^d	None
Current smoker (%)	30**	20	33***	15	35	31	25	18

Data are presented as the mean±SD, median (25th–75th) or percentage

NA: not available, MA: microalbuminuria (defined as AER 20–200 μg/min in at least two of three timed urine samples)

*p<0.05; **p<0.01; ***p<0.001

[a] Significant only in men; [b] Significant only in women

[c] Normal ranges: HbA$_{1c}$ (DCCT/EDIC), 4.5–6.1%; GHb (EURODIAB), 2.9–4.8%; GHbA$_1$ (Lehto et al. [6]), 5.5–8.5%; HbA$_1$ (EDC), 4.9–7.3%

[d] Study exclusion criterion

tocol using a random-zero sphygmomanometer (Hawksley, Lancing, UK) [18]. Hypertension was defined as BP≥140/ 90 mmHg or use of medication specifically to lower BP. Estimated glucose disposal rate (eGDR), a measure of insulin sensitivity, was calculated using a regression equation derived from hyperinsulinaemic–euglycaemic clamp studies using HbA$_1$, waist to hip ratio (WHR) and hypertension [19]. Fasting blood samples were taken for analysis of lipids, lipoproteins, serum creatinine and glycosylated Hb. HDL-cholesterol was determined by a precipitation technique (heparin and manganese chloride) with a modification [20] of the Lipid Research Clinics method [21]. Total cholesterol and triacylglycerol were measured enzymatically [22, 23]. LDL-cholesterol levels were calculated from measurements of the levels of total cholesterol,

triacylglycerol and HDL-cholesterol using the Friedewald equation [24]. For the first 18 months, fasting blood samples were analysed for HbA$_1$ (microcolumn cation exchange; Isolab, Akron, OH, USA). For the remainder of the 10 year follow-up, automated HPLC (Diamat; BioRad, Hercules, CA, USA) was performed. The two assays were highly correlated (r=0.95; Diamat [HbA$_1$]=−0.18+1.00 [Isolab HbA$_1$]). For follow-up beyond 10 years, HbA$_{1c}$ was measured with the DCA 2000 analyser (Bayer, Tarrytown, NY, USA); the DCA and Diamat assays were also highly correlated (r=0.95; DCA [HbA$_{1c}$]=−0.618+0.846 [Diamat HbA$_1$]). Height and weights were measured during clinic visits and BMI was calculated as height (cm)/weight (kg)^2. Timed urine samples were assayed for albumin by immunoelectrophoresis [16, 25]. Macroalbuminuria was defined as

AER>200 μg/min and microalbuminuria as 20–200 μg/min in at least two of three timed urine samples.

CAD outcomes

CAD cases were defined as EDC-diagnosed angina, myocardial infarction (Minnesota Codes 1.1, 1.2), ischaemic ECG (Minnesota Codes 1.3, 4.1–4.3, 5.1–5.3, 7.1), revascularisation and fatal myocardial infarction. Baseline ECGs were coded using the Minnesota Code [26].

Statistical analysis

Sixteen year follow-up Differences between CAD cases and non-cases were evaluated using Student's t test and the χ^2 test. Non-normally distributed variables (i.e. AER, triacylglycerol, serum creatinine) were transformed by natural log; the Mann–Whitney U test was used to compare continuous variables that could not be log-normalised (as indicated). A significance level of $p<0.05$ was considered statistically significant. Because of colinearity with diabetes duration ($r=0.86$), age was not used in multivariable analyses. Analyses were performed using SPSS for Windows software (SPSS, Chicago, IL, USA).

HbA$_{1c}$ change analysis All EDC HbA$_1$ and HbA$_{1c}$ values were converted to a DCCT standard HbA$_{1c}$ value using regression equations derived from duplicate assays. For the original 10 year EDC follow-up, HbA$_1$ values were converted using the equation: DCCT HbA$_{1c}$=(0.83× EDC HbA$_1$)+0.14. After the 10 year examination the DCA HbA$_{1c}$ assay values were converted to the DCCT standard HbA$_{1c}$ using the equation: DCCT HbA$_{1c}$=(EDC HbA$_{1c}$−1.13)/0.81. Change in HbA$_{1c}$ from baseline to the examination prior to CAD incidence, or at censoring, was calculated by subtracting the baseline value from the final value. A comparison of change in HbA$_{1c}$ between CAD cases ($n=97$) and non-cases ($n=374$) was completed using the t test. Changes in other risk factors (e.g. non-HDL- and HDL-cholesterol, BMI, AER), were calculated in a similar manner. The new use of treatments, such as use of antilipidaemic agents, angiotensin-converting enzyme (ACE) inhibitors or intensive insulin therapy, was determined by comparing use at baseline with that at the follow-up cycle. Intensive insulin therapy was defined as at least three insulin injections per day or the use of an insulin pump. Univariate and multivariable logistic regressions were performed to examine the relationship between CAD incidence and independent variables, including HbA$_{1c}$. Variables entered a model if univariately significant at $p<0.10$ and were retained in the model at $p<0.05$. Odds ratios are expressed per SD for continuous variables.

Results

Comparison study

Baseline characteristics of CAD cases and non-cases for each study population are presented in Table 1. With the exception of the Lehto et al. study [6], a mix of prevalent and incident CAD cases, all cases were incident. The EDC results update, with 16 years of follow-up data, those previously published after 10 years of follow-up [10]. Significant univariate predictors of CAD (CVD in DCCT/EDIC) shared among study populations were age and diabetes duration, although in the Lehto et al. study age was significant only in men and diabetes duration only in women. AER, although not available for the Lehto et al. population (renal disease was an exclusion criterion), was also a univariate predictor in the other three studies. With the exception of the Lehto et al. study, elevated total and LDL-cholesterol and triacylglycerol levels were observed in CAD/CVD cases across these three populations, whereas HDL-cholesterol differed only in EDC. Hypertension contributed to CAD in EDC and EURODIAB but not in the Lehto et al. study, and was an exclusion criterion in DCCT/EDIC. Baseline glycohaemoglobin levels were significantly higher in CVD cases in DCCT/EDIC ($p<0.05$) and in men (but not women) in the Lehto et al. study. No association was seen in EDC or EURODIAB.

HbA$_{1c}$ change analyses

Baseline characteristics and univariate CAD predictors in the HbA$_{1c}$ change study population are presented in Table 2. Incident CAD cases were older and had a longer diabetes duration, higher non-HDL-cholesterol level and lower HDL-cholesterol level compared with non-cases ($p<0.001$). CAD cases also had higher WHR, BP and pulse rate and were more likely to have hypertension or albuminuria, and to be current or former smokers. Whereas baseline HbA$_{1c}$ levels were similar between CAD cases and non-cases ($p=0.62$), mean change in HbA$_{1c}$ increased among CAD cases but decreased among non-cases (+0.62± 1.8 vs −0.09±1.8%, $p<0.001$).

Participants were further categorised by degree of change from baseline to event (CAD cases) or censoring (non-cases). Those whose change was within 1 SD were considered stable, whereas those with a decrease or increase of ≥1 SD were considered 'fallers' and 'risers' respectively. The percentage of CAD cases within each category increased across the faller, stable and riser groups. The CAD incidence densities for the faller, stable and riser groups were 1.4, 4.3 and 8.0 per 100 patient-years respectively (Fig. 1).

Table 2 Baseline characteristics and risk factor change by CAD incidence status in the EDC study/HbA$_{1c}$ change population

Variable	CAD	
	Yes	No
n	97	372
Baseline characteristics		
Sex (% male)	58.8	50.5
Age (years)	32.2±6.6***	25.4±7.3
Duration of disease (years)	24.2±6.8***	17.2±6.7
BMI (kg/m^2)	24.0±3.3	23.4±3.3
Systolic BP (mmHg)	117.9±15.1***	110.9±13.1
Diastolic BP (mmHg)	75.8±11.1***	70.9±10.0
Hypertension (%)	32.0**	18.0
Serum creatinine (μmol/l)	88.4±45.1*	84.9±82.2
Total cholesterol (mmol/l)	5.35±1.12***	4.74±0.99
HDL-cholesterol (mmol/l)	1.29±0.28***	1.43±0.31
LDL-cholesterol (mmol/l)	3.38±0.97***	2.82±0.80
Triacylglycerol (mmol/l)	1.51±1.06***	1.06±0.75
Non-HDL-cholesterol (mmol/l)	1.44±0.42***	1.77±0.51
AER (μg/min)	4,203.6± 9,865.1***	1,312.3± 4,288.0
Pulse (beats per min)	79.3±9.6***	77.1±9.2
Microalbuminuria status (%)	64.9***	35.8
Current smoker (%)	28.4*	18.5
Ever smoked (%)	49.0**	31.7
WHR	0.85±0.07***	0.82±0.07
eGDR	7.1±2.0***	8.2±1.7
White blood cell count (×10^9/l)	8.1±9.7	6.7±7.1
Baseline HbA$_{1c}$ (%)	8.8±1.6	8.7±1.5
Risk factor changes		
Change in HbA$_{1c}$ (%)	0.62±1.8***	−0.09±1.9
Change in systolic BP (mmHg)	6.3±17.3	7.7±15.5
Change in diastolic BP (mmHg)	−0.39±11.8	2.7±43.2
Became hypertensive (%)	15.7	17.1
Change in eGDR	−1.2±1.9	−0.84±1.9
Change in BMI (kg/m^2)	0.70±2.1***	2.3±3.1
Change in HDL-cholesterol (mmol/l)	−0.002±0.23	0.012±0.31
Change in non-HDL-cholesterol (mmol/l)	−0.025±1.1*	0.275±1.0
Change in triacylglycerol[a] (mmol/l)	0.073±1.50	0.110±0.95
Change in AER[a] (μg/min)	157.8±1,334.5*	334.4± 5,242.8
New anti-lipidaemic agent (%)	4.2	10.7*
New ACE inhibitor (%)	20.6	26.9
Went on intensive insulin therapy (%)	14.7	36.4***

Data are presented as the mean±SD or percentage

*ACE*: angiotensin-converting enzyme

*$p<0.05$; **$p<0.01$; ***$p<0.001$

[a] Log-transformed for comparison between groups

Significant univariate CAD predictors previously identified [10] and those from Table 2 were considered for multivariable analyses. In multivariable logistic regression analyses, only diabetes duration, HDL-cholesterol and non-HDL-cholesterol and change in HbA$_{1c}$ remained significant predictors (Table 3). When baseline HbA$_{1c}$ was factored into the model, it also became a significant positive predictor and change in HbA$_{1c}$ remained significant (Model 2). Further adjustment, however, for renal disease and BMI change eliminated baseline HbA$_{1c}$ (Models 3 and 4). No significant interaction was observed between HbA$_{1c}$ change and baseline HbA$_{1c}$.

The characteristics of risers and fallers were also examined. Risers were older, had longer diabetes duration, saw their doctor more frequently, and had a more adverse profile of CAD risk factors than fallers had. Though age, diabetes duration, triacylglycerol, WHR, eGDR and micro-albuminuria showed similar case/non-case differences ($p<0.05$ for all variables) in fallers and risers, CAD cases in the riser group also showed major differences compared with non-cases in non-HDL-cholesterol, AER, macro-albuminuria, HDL-cholesterol, BP and white blood cell count ($p<0.01$ for all variables), while among fallers the CAD cases had significantly higher serum creatinine levels ($p<0.05$) (Table 4). These results are thus generally consistent with the multivariate analysis (Table 3).

Discussion

The findings from the published literature (Table 1) suggest that the association of glycaemia with CAD is much stronger in type 1 diabetes when renal disease is not present. This assertion, based on the observation that the only strong epidemiological glycaemia–CAD link was in the Lehto et al. study [6] of participants without renal disease, is also consistent with the DCCT/EDIC trial data. In DCCT/EDIC, a reduction in the risk of CVD events in the intensive insulin therapy group was reported, where both a fall in HbA$_{1c}$ occurred and renal disease was less
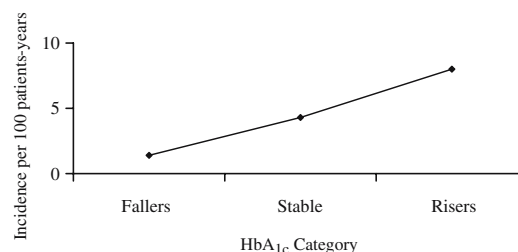
Fig. 1 Incidence of coronary artery disease per 100 patient-years by HbA$_{1c}$ change category in the EDC study. Fallers: a fall of 1 SD or greater; Risers: a rise of 1 SD or greater; Stable: change within ±1 SD

Table 3 Regression models for prediction of coronary artery disease over 16 years of follow-up in the EDC/HbA$_{1c}$ change population

	Model 1	Model 2	Model 3[a]	Model 4[a]
Duration	2.80 (2.11–3.07)***	2.86 (2.14–3.82)***	3.24 (2.35–4.45)***	3.10 (2.24–4.30)***
Non-HDL-cholesterol	1.63 (1.28–2.08)***	1.55 (1.18–2.04)***	1.80 (1.33–2.44)***	1.72 (1.24–2.39)**
HDL-cholesterol	0.60 (0.45–0.81)***	0.61 (0.45–0.82)***	0.73 (0.54–0.99)***	0.74 (0.54–1.00)
Change in HbA$_{1c}$	NA	1.73 (1.26–2.38)***	1.55 (1.08–2.21)*	1.51 (1.05–2.17)*
Baseline HbA$_{1c}$	NA	1.44 (1.03–2.02)*	1.04 (0.71–1.53)	0.98 (0.67–1.45)
Change in AER	NA	NA	1.26 (1.04–1.54)*	1.32 (1.08–1.61)**
Change in BMI	NA	NA	0.61 (0.44–0.84)**	0.61 (0.44–0.85)**
Baseline AER	NA	NA	NA	1.26 (0.95–1.68)
Baseline BMI	NA	NA	NA	0.86 (0.64–1.16)
Akaike information criterion	373.322[b]	364.701[b]	311.098[c]	305.496[c]

Data are presented as the odds ratio (95% CI), except for the Akaike information criterion

Odds ratios are calculated per SD

Model 1 allowed for diabetes duration, non-HDL-cholesterol, HDL-cholesterol, baseline HbA$_{1c}$, hypertension status (HTN), AER, BMI, serum creatinine, sex and smoking status (ever smoked)

Model 2 allowed for diabetes duration, non-HDL-cholesterol, HDL-cholesterol, change in HbA$_{1c}$, hypertension, AER, BMI, serum creatinine, sex and smoking status (ever smoked). Baseline HbA$_{1c}$ forced

Model 3 allowed for diabetes duration, non-HDL-cholesterol, HDL-cholesterol, change in HbA$_{1c}$, hypertension, AER, BMI, serum creatinine, sex, smoking status (ever smoked), change in non-HDL-cholesterol, change in BMI and change in AER. Baseline HbA$_{1c}$ forced

Model 4 allowed for diabetes duration, non-HDL-cholesterol, HDL-cholesterol, change in HbA$_{1c}$, hypertension, AER, BMI, serum creatinine, sex, smoking status (ever smoked), change in non-HDL-cholesterol, change in BMI and change in AER. Adjusted for baseline HbA$_{1c}$, baseline BMI and baseline AER

*p<0.05; **p<0.01; ***p<0.001

[a] Multivariable analyses for change in other risk factors, n=437

[b] Akaike information criterion for models 1 and 2, n=469; [c] Akaike information criterion for models 3 and 4, n=437

apparent [13]. The present EDC analyses also suggest that change in glycaemia is a predictor even when baseline or mean HbA$_{1c}$ during follow-up is not. We are unaware of any previous epidemiological reports demonstrating this latter finding in type 1 diabetes, though the DCCT/EDIC data would, a priori, be consistent.

Our exploration of the effect of change in glycaemia (as opposed to either baseline or mean glycaemia over time) on

Table 4 Differences in baseline risk factors for CAD in those with a lowering of HbA$_{1c}$ over time (fallers) and those with an increase in HbA$_{1c}$ (risers) in the Pittsburgh Epidemiology of Diabetes Complications study/HbA$_{1c}$ change population

Incident CAD	Fallers		Risers	
	CAD$^+$ (n=11)	CAD$^-$ (n=79)	CAD$^+$ (n=32)	CAD$^-$ (n=67)
Age (years)	30.5±6.9**	24.3±7.1	32.9±6.2***	25.6±7.6
Disease duration (years)	22.8±7.5**	16.3±6.4	25.1±6.7***	17.9±6.8
Sex (% male)	72.7	49.4	62.5	49.3
Non-HDL-cholesterol (mmol/l)	4.09±0.71	1.18±1.18	4.35±1.25***	3.07±0.75
HDL-cholesterol (mmol/l)	1.29±0.19	1.47±0.29	1.26±0.31**	1.50±0.35
Systolic BP (mmHg)	111.7±15.3	110.6±10.9	120.5±15.4**	111.7±11.4
Diastolic BP (mmHg)	72.9±10.2	72.3±10.8	76.8±10.1***	69.0±8.8
AER (μg/min)	484.9 (294.1–7,799.9)	118.6 (63.2–799.0)	994.3 (57.1–3,947.2)***	78.4 (41.3–255.4)
White blood cell count (×10^9/l)	6.4±1.6	6.4±1.9	7.5±2.2*	6.4±2.0
Serum creatinine (μmol/l)	97.2 (70.7–97.2)*	79.6 (53.0–88.4)	88.4 (61.9–97.2)	70.7 (61.9–88.4)
Hypertension (%)	18.2	26.6	37.5**	14.2
Current smoker (%)	18.2	26.6	37.5**	14.8
≥Microalbuminuria (%)	81.8*	40.5	71.9***	34.3
≥Macroalbuminuria (%)	60.0	26.6	60.9***	18.5

Data are presented as the mean±SD, median (25th–75th percentile) or percentage

Microalbuminuria was defined as AER 20–200 μg/min in at least two of three timed urine samples

Macroalbuminuria was defined as AER >200 μg/min in at least two of three timed urine samples

*p<0.05; **p<0.01; ***p<0.001

CAD risk shows that a 1% decrease in HbA_{1c} was associated with a 23% decrease in CAD risk. Also of interest is that, while baseline HbA_{1c} alone was not related to CAD, when factored into the model with HbA_{1c} change it became significant. Nonetheless, further adjustment for renal disease and BMI change during follow-up completely eliminated any association between baseline HbA_{1c} and CAD incidence (Table 3). The protective effect of BMI change (i.e. an increase) is consistent with the intensification of insulin therapy and our previous report that weight gain in the presence of good glycaemic control is linked to an improved risk factor profile [27].

The underlying mechanism leading to the effect of change in HbA_{1c} on CAD risk, in the absence of a strong direct baseline association, is intriguing. It is possible that exposure to a noxious agent such as hyperglycaemia leads to activation of a number of defence (e.g. anti-inflammatory) mechanisms and that a decrease in exposure (as experimentally in DCCT/EDIC or observationally in EDC) leaves the participant in a hyperprotected state. An example is the 'protective' effect of previous smoking on the risk of thromboembolism after myocardial infarction in the era when bed rest was the primary therapy [28]. This has been explained by smokers having activated antithrombolytic/fibrinolytic mechanisms in response to smoking and thus after a myocardial infarction (when they no longer smoke) are better placed to counteract the effect of bed rest on venous thrombosis. Similarly, recurrence of venous thromboembolism was less likely in women who were on oral contraceptives and stopped using them than in women who had their first incident in the absence of oral contraceptives [29]. Thus, change itself may also reflect the previous response to a noxious stimulus (e.g. glycaemia) as well as the difference in exposure.

The CAD/CVD risk factors common among all four studies compared here were diabetes duration and age. However, it is striking that duration at baseline in DCCT/EDIC was much shorter than in the other studies. Also of note is that traditional cardiovascular risk factors, such as lipid/lipoprotein levels, hypertension and smoking status, were not significant predictors of CAD events in the Lehto et al. study, in which diabetes duration, a history of myocardial infarction and HbA_1 were the only significant risk factors. This smaller study, with a shorter follow-up, was quite different from the other studies; it excluded persons with renal disease (which has been shown to increase the risk of CAD death [30] and may, historically, be associated with >80% of CAD in type 1 diabetes [31]), but did include those with previous cardiovascular events. Also unique is that it comprised patients with a much older age of diabetes onset (>29 years). This study thus raises the intriguing possibility that 'non-renal CAD' in type 1 diabetes may have a more predominant glycaemic aetiology,

as illustrated in Fig. 2. As indicated above, this may also relate to the stronger benefit of glycaemic control in DCCT/EDIC, where renal disease was markedly less prevalent than in EDC or EURODIAB. An alternative possibility is that the renal effect on CAD risk may be so great that it overpowers the effect of glycaemia per se in the epidemiology studies, though previous EDC analyses suggest this is unlikely [32].

Total cholesterol, LDL-cholesterol and triacylglycerol levels were significant univariate risk factors for CAD/CVD in EDC, EURODIAB and the DCCT/EDIC, in which baseline hypercholesterolaemia was an exclusion criterion. Baseline hypertension (BP≥140/90) was also a significant CAD risk factor in both EDC and EURODIAB but was also an exclusion criterion in the DCCT/EDIC and did not predict CVD events.

The study comparison in Table 1 used only baseline glycohaemoglobin levels while the main DCCT/EDIC effect resulted from the intervention, represented by a lower mean HbA_{1c} during the trial [14]. It thus could be hypothesised that baseline HbA_{1c} is not sufficient to account for the relationship between glycaemia and CAD. In our Pittsburgh EDC study we explored the effect of cumulative glycaemic exposure using a calculated variable, A1 months (months of exposure to different, above-normal, HbA_1 levels). This, despite being highly predictive of microvascular complications, did not predict CAD [11, 32]. Nevertheless, it is important to note that the level of glycaemia in EDC, though comparable with that in the conventional therapy group in DCCT/EDIC, was much higher during follow-up than in the intensive therapy group. It is possible therefore that the benefit of good glycaemic control may not be evident unless mean HbA_{1c} levels are as low as the 7.2% achieved in DCCT.

One limitation of this study is the use of three methods for assessing HbA_1/HbA_{1c} level over the 16 year follow-up period. Though this was unavoidable as the technology was in development, it is likely to have introduced noise into the assessment. This is, however, more likely to weaken relationships than lead to spurious results. Another limitation is that the time between the HbA_{1c} levels used to calculate the change in HbA_{1c} varied according to the timing of events. In addition, the difference between baseline and follow-up HbA_{1c} was calculated using only
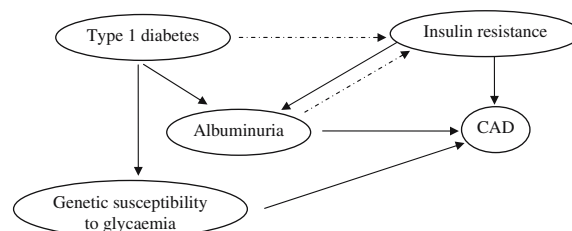
Fig. 2 Proposed mechanisms involved in the development of CAD in type 1 diabetes

two HbA_{1c} measurements, which may not therefore fully account for changes and fluctuations throughout follow-up. These limitations again, however, would apply similarly to those with and without incident CAD and would be more likely to weaken the findings reported than spuriously cause them.

In conclusion, the differences between the epidemiological studies and the DCCT/EDIC results concerning the relationship between glycaemia and CAD are very likely to be due to major differences among the study populations. In particular, the prevalence of renal disease may be important, as in its absence glycaemia appears a major predictor. Change in HbA_{1c}, as opposed to glycaemic exposure per se, may also be important, as an effect of HbA_{1c} change over time is a finding common to both the DCCT/EDIC trial and the observational EDC study. The possibility that this may in part reflect the body's enhanced response to hyperglycaemia as well as a direct noxious effect of glycaemia itself merits further study.

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