Coprogression of Cardiovascular Risk Factors in Type 1 Diabetes During 30 Years of Follow-up in the DCCT/EDIC Study

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OBJECTIVE

The Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study has demonstrated the beneficial effect of intensive therapy on atherosclerosis and clinical cardiovascular outcomes, while identifying hyperglycemia as a dominant risk factor for type 1 diabetes. The current analyses evaluate the extent to which glycemic exposure influences long-term changes in established risk factors for cardiovascular disease (CVD) among patients with type 1 diabetes.

RESEARCH DESIGN AND METHODS

The DCCT study randomized 1,441 participants to receive intensive or conventional diabetes therapy; and after an average of 6.5 years of follow-up, 96% of the surviving cohort enrolled in the EDIC observational study for an additional 20 years of follow-up. Annual visits included a detailed medical history and physical examination. Blood and urine samples were collected and assayed centrally. Longitudinal models for repeated measurements were used.

RESULTS

Higher HbA_{1c} level was a significant correlate of the longitudinal changes in all of the traditional CVD risk factors over the 30-year follow-up. The strongest longitudinal associations were among the lipid measurements and concurrent glycemia.

CONCLUSIONS

A better understanding of the interrelationships between diabetes-related risk factors and traditional CVD risk factors may assist with the development of targeted treatment regimens for persons with type 1 diabetes who are at risk for CVD.

Type 1 diabetes has been associated with an increased risk of cardiovascular disease (CVD) morbidity and mortality (1). Despite improvements in risk factor profiles and robust treatment recommendations aimed at preventing diabetes-related complications, CVD remains the leading cause of death among individuals with type 1 diabetes (2,3), and increased risk of CVD is a major health concern.

The Diabetes Control and Complications Trial (DCCT) and its follow-up the Epidemiology of Diabetes Interventions and Complications (EDIC) study demonstrated the beneficial effect of intensive therapy on atherosclerosis and major CVD events

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**A list of the members of The Writing Group for the DCCT/EDIC Research Group appears in the APPENDIX and a complete list of participants in the DCCT/EDIC Research Group is presented in the Supplementary Appendix to the article in N Engl J Med 2015;372:1722–1733.*

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(2,4–6). The analyses demonstrated that hyperglycemia was a major risk factor for CVD in type 1 diabetes. However, there have been few studies with robust long-term data published evaluating the influence of levels of hyperglycemia in individuals with type 1 diabetes on changes in established CVD risk factors, such as lipids or blood pressure. The DCCT/EDIC study provides the opportunity to explore the interrelationships of traditional CVD risk factors and glycemia in a carefully studied cohort of patients with type 1 diabetes over an extended period of time.

Herein we describe the long-term changes in CVD risk factors observed over a 30-year period of follow-up in the DCCT/EDIC study. The aims are to evaluate the association of glycemic exposure with CVD risk factors and their coprogression, and to describe differences in CVD risk factors between the original DCCT intensive treatment and conventional treatment groups. Delineating the relationship between glycemia and traditional CVD risk factor progression over time may prove beneficial to understanding macrovascular disease in type 1 diabetes as well in providing insight for preventive treatment regimens.

RESEARCH DESIGN AND METHODS

Detailed descriptions of the DCCT intervention and the EDIC observational follow-up study have been published previously (7–9). Briefly, 1,441 subjects with type 1 diabetes were enrolled in the DCCT between 1983 and 1989. Approximately half of the cohort (N = 711) was randomized to receive intensive therapy with a goal of safely maintaining blood glucose levels within a near-normal nondiabetic range. The remainder (N = 730) were assigned to conventional therapy with a goal of clinical well-being and freedom from symptoms related to both hyperglycemia and hypoglycemia. The following two parallel cohorts were recruited: the primary prevention cohort (N = 726), with diabetes duration of 1–5 years, no retinopathy (microaneurysms or worse), and a urine albumin excretion rate (AER) $<$40 mg/24 h; and the secondary intervention cohort (N = 715), with diabetes duration of 1–15 years, mild to moderate nonproliferative diabetic retinopathy, and an AER of $\leq$200 mg/24 h. Subjects with a history of CVD or with hypertension (blood pressure $>$140/90 mmHg or receiving medication) or hyperlipidemia (fasting serum cholesterol level $\geq$3 SDs above age- and sex-specific means) were not eligible to participate.

After an average of 6.5 years (range 3–9) of follow-up, 1,422 subjects completed a closeout visit (99% of the original cohort). Subjects who were originally assigned to receive conventional treatment were encouraged to adopt intensive therapy, and subjects in both groups were returned to receive care from their own health care providers. In 1994, 96% of the surviving DCCT cohort enrolled in the EDIC observational study, and after an additional 20 years of follow-up, 1,251 participants (94% of the surviving cohort) continue to be followed.

Evaluations

Although more frequent medical visits occurred during the DCCT, the present analyses focus only on the data obtained at annual visits during both the DCCT and the EDIC study. In longitudinal analyses, study years 0 through 9 represent the DCCT, and years 10 through 30 the EDIC follow-up study. Owing to staggered entry into the DCCT and the fixed DCCT duration, the numbers evaluated decline over DCCT years 5–9.

Each annual visit included a detailed medical history including demographic and behavioral risk factors, medical outcomes, and a physical examination, which included measurements of height, weight, sitting blood pressure, and pulse rate (7,9). Pulse pressure was defined as the difference between the systolic and diastolic blood pressure readings. Blood samples were collected at each annual visit and were assayed centrally for HbA_{1c}, using high-performance ion-exchange liquid chromatography. Fasting lipids (triglycerides, total, and HDL cholesterol) were measured annually during DCCT and in alternate years during the EDIC study, and were evaluated centrally (10). LDL cholesterol was calculated using the Friedewald equation (11). Concurrent medication usage was collected during the EDIC study, but not during the DCCT. However, the current cardiorenal protective agents were either unavailable (statins, angiotensin receptor blockers) or not prescribed according to protocol (ACE inhibitors) during the DCCT.

Classification of CVD Risk Factors

For this analysis, risk factors were classified into the following four major categories: protocol dictated (DCCT treatment group, primary prevention vs. secondary intervention cohort); demographic (sex, age, weight, BMI, smoking, drinking alcohol, physical activity, family history of hypertension, myocardial infarction, type 1 and type 2 diabetes); traditional (blood pressure, pulse pressure, pulse rate, total cholesterol, triglycerides, and HDL and LDL cholesterol); and diabetes related (diabetes duration, stimulated C-peptide level, estimated glucose disposal rate, and HbA_{1c} level) (Table 1). Weight and BMI were evaluated separately in men and women. In addition to the current HbA_{1c} value, the DCCT updated mean was used to reflect the cumulative glycemic exposure from baseline up to and including the HbA_{1c} at each visit throughout the DCCT. The DCCT/EDIC study time-weighted arithmetic mean was calculated using the quarterly DCCT values and the annual EDIC study values weighted by 3 and 12 months, respectively.

Statistical Analyses

At DCCT baseline, quantitative and categorical characteristics were compared between treatment groups using the Wilcoxon rank sum test and χ^2 test, respectively. Generalized linear mixed models were used to assess covariate effects on the mean of each quantitative risk factor over repeated time points, and generalized estimating equation models were used to assess effects on the prevalence of each binomial risk factor. The DCCT/EDIC study year (time 0–9 years representing the DCCT, and 10–30 years representing the EDIC study) was included as a class effect. The models assumed an unstructured covariance structure, or, in cases where the model did not converge, a heterogeneous compound symmetry structure. Covariates measured repeatedly over time entered the models as time-dependent covariates. Pearson correlation coefficients were used to evaluate the associations among each of the protocol-dictated, demographic, traditional, and diabetes-related risk factors at the DCCT baseline. Additionally, a comprehensive analysis of collinearity was completed (12).

The signed t statistic was used as a measure of the magnitude and direction

Table 1—Clinical characteristics of the DCCT/EDIC study cohort by treatment group assignment at DCCT baseline (1983–1989) and by the 30th year of DCCT/EDIC study follow-up (2013)

		DCCT baseline (1983–1989)			Average over DCCT/EDIC		
		Intensive treatment (*N* = 711)	Conventional treatment (*N* = 730)	*P* value*	Intensive treatment (*N* = 711)	Conventional treatment (*N* = 730)	*P* value*
Protocol	Cohort (% primary prevention)†	49	52	0.2818			
Demographic							
Physical	Sex (% women)†	49	46	0.3169			
	Age (years)‡	27 ± 7	27 ± 7	0.1383	41 ± 8	40 ± 8	**0.0141**
	Adult (%)†	87	86	0.5162			
	Weight (kg)‖						
	Men	73.8 ± 10.8	75.8 ± 11.7	**0.0091**	89.0 ± 10.6	83.9 ± 10.8	**<0.0001**
	Women	62.7 ± 8.6	62.1 ± 9.5	0.2966	74.3 ± 9.5	70.4 ± 9.4	**<0.0001**
	BMI (kg/m^2)‖						
	Men	23.4 ± 2.6	23.9 ± 2.9	**0.0045**	27.7 ± 2.8	26.6 ± 2.9	**<0.0001**
	Women	23.3 ± 2.8	22.9 ± 2.9	0.0610	27.3 ± 3.2	26.0 ± 3.2	**<0.0001**
Behavioral	Current cigarette smoker (%)	19	18	0.9718	17	17	0.9982
	Occasional or regular drinker (%)	21	22	0.4852	39	41	0.3492
	Moderate or strenuous activity (%)	70	69	0.6880	56	56	0.9455
Family history	Family history (%)†						
	Hypertension	57	56	0.8445			
	Myocardial infarction	48	49	0.6459			
	Type 1 diabetes	14	14	0.8025			
	Type 2 diabetes	10	8	0.4238			
Traditional							
Blood pressure	Systolic (mmHg)	113 ± 12	115 ± 12	**0.0116**	119 ± 8	119 ± 9	0.4321
	Diastolic (mmHg)	72 ± 9	73 ± 9	0.2574	74 ± 5	74 ± 5	0.7303
	Pulse pressure (mmHg)	41 ± 10	42 ± 10	0.0639	45 ± 6	45 ± 6	0.3492
Pulse rate	Rate (bpm)	76 ± 11	76 ± 11	0.7269	72 ± 7	73 ± 7	**0.0094**
Lipid	Total cholesterol (mg/dL)	177 ± 33	176 ± 34	0.5289	181 ± 25	183 ± 25	0.1216
	Triglycerides (mg/dL)	81 ± 43	82 ± 51	0.8151	72 ± 27	77 ± 27	**0.0002**
	HDL cholesterol (mg/dL)	51 ± 12	50 ± 12	0.5048	56 ± 11	56 ± 11	0.7699
	LDL cholesterol (mg/dL)	110 ± 29	109 ± 29	0.4967	108 ± 22	109 ± 22	0.2948
Diabetes related							
History	Duration of diabetes (years)‡	6 ± 4	5 ± 4	0.1441	20 ± 5	19 ± 5	**0.0108**
	Stimulated C-peptide (nmol/L)†¶						
	Duration <60 months	0.16 ± 0.13	0.16 ± 0.13	0.5482			
	Duration ≥60 months	0.04 ± 0.03	0.04 ± 0.04	0.0689			
	eGDR†				7.4 ± 1.8	7.3 ± 1.9	0.3798
Glycemia	HbA_{1c} (%)	9.1 ± 1.6	9.1 ± 1.6	0.5542	7.8 ± 1.0	8.5 ± 1.0	**<0.0001**
	HbA_{1c} (mmol/mol)	75.8 ± 17.4	75.5 ± 17.9		61.5 ± 10.4	69.0 ± 10.5	

Data are reported as the mean ± SD or %. eGDR, estimated glucose disposal rate. Boldface type indicates *P* values that are significant at the $P < 0.05$ level. *At DCCT baseline, treatment group comparisons were made using the Wilcoxon rank sum test or the χ^2 test. For characteristics repeated over time (e.g., weight or percentage of smokers), the average mean or prevalence over 30 years of DCCT/EDIC study annual follow-up was computed using longitudinal generalized estimating equations (GEEs) for repeated measures. SDs were estimated from the SEs using the following equation, SD = SE*SQRT(*N*). The SDs are smaller during the DCCT/EDIC study follow-up period owing to the larger amount of information in the longitudinal models. †Cohort, sex, adult, and family history are fixed baseline characteristics. C-peptide level data were not collected during the EDIC study. Waist data used to calculate eGDR were not measured during the DCCT. ‡Age and duration were not evaluated using longitudinal GEE models because each is a function of time itself. Instead, the average age and duration were computed for each subject over that subject's length of follow-up. The average mean value over all subjects and its SD are presented. Treatment group comparisons were made using the Wilcoxon rank sum test. ‖Data for men were based on 366 intensive treatment and 395 conventional treatment participants; data for women were based on 345 intensive treatment and 335 conventional treatment participants. ¶Data for duration <60 months based on 412 intensive treatment and 443 conventional treatment participants; data for duration of ≥60 months based on 299 intensive treatment and 287 conventional treatment participants.

of the association between an outcome and a covariate. Models were fit without HbA_{1c} level and then by simultaneously adjusting for HbA_{1c} level as a time-dependent covariate in order to evaluate the mediating effect of HbA_{1c} level. All analyses were performed using SAS software (version 9.3; SAS Institute, Cary, NC). A two-sided *P* value ≤0.05 was considered to be statistically significant.

RESULTS

Participant Characteristics

The characteristics of the DCCT/EDIC study participants at baseline and after 30 years of follow-up are presented in Table 1. There were no major differences between the intensive treatment and conventional treatment groups at DCCT baseline, except for a 2 mmHg higher systolic blood pressure and a 2-kg higher weight in men in the conventional group. Over the course of the entire 30-year study period, subjects in the conventional treatment group had a higher overall mean pulse rate (73 ± 7 vs. 72 ± 7 bpm, *P* = 0.0094) over all visits combined, a higher triglyceride level (77 ± 27 vs. 72 ± 27 mg/dL, *P* = 0.0002), and higher HbA_{1c} level (8.5 ± 1.0% vs. 7.8 ± 1.0%, *P* < 0.0001). The difference in mean HbA_{1c} level was largely accounted for by the lower HbA_{1c} level maintained by design in the intensive treatment group during the DCCT. Men and women in the intensive treatment group had a 5- and 4-kg higher mean weight, respectively, over the duration of the study compared with conventionally treated men and women (*P* < 0.0001).

There were strong correlations between systolic and diastolic blood pressure, and between total and LDL cholesterol values (data not shown). Thus, the subsequent risk factor models did not include total cholesterol. Other pairs of variables such as diabetes duration/cohort (primary prevention vs. secondary intervention) and weight/BMI were highly correlated by definition. However, a test of collinearity did not identify any concerns.

Long-term Changes in Risk Factors

Figure 1 presents the mean ± SE for each of the quantitative risk factors over time along with the prevalence of any relevant medication use during EDIC study. During the DCCT, there was a substantially greater increase in weight in the intensive versus conventional treatment group, and more so among women (Fig. 1). This group difference in weight among women persisted during the EDIC study, whereas there was a negligible group difference among men in the EDIC study.

Systolic blood pressure increased steadily over the 30-year period, while

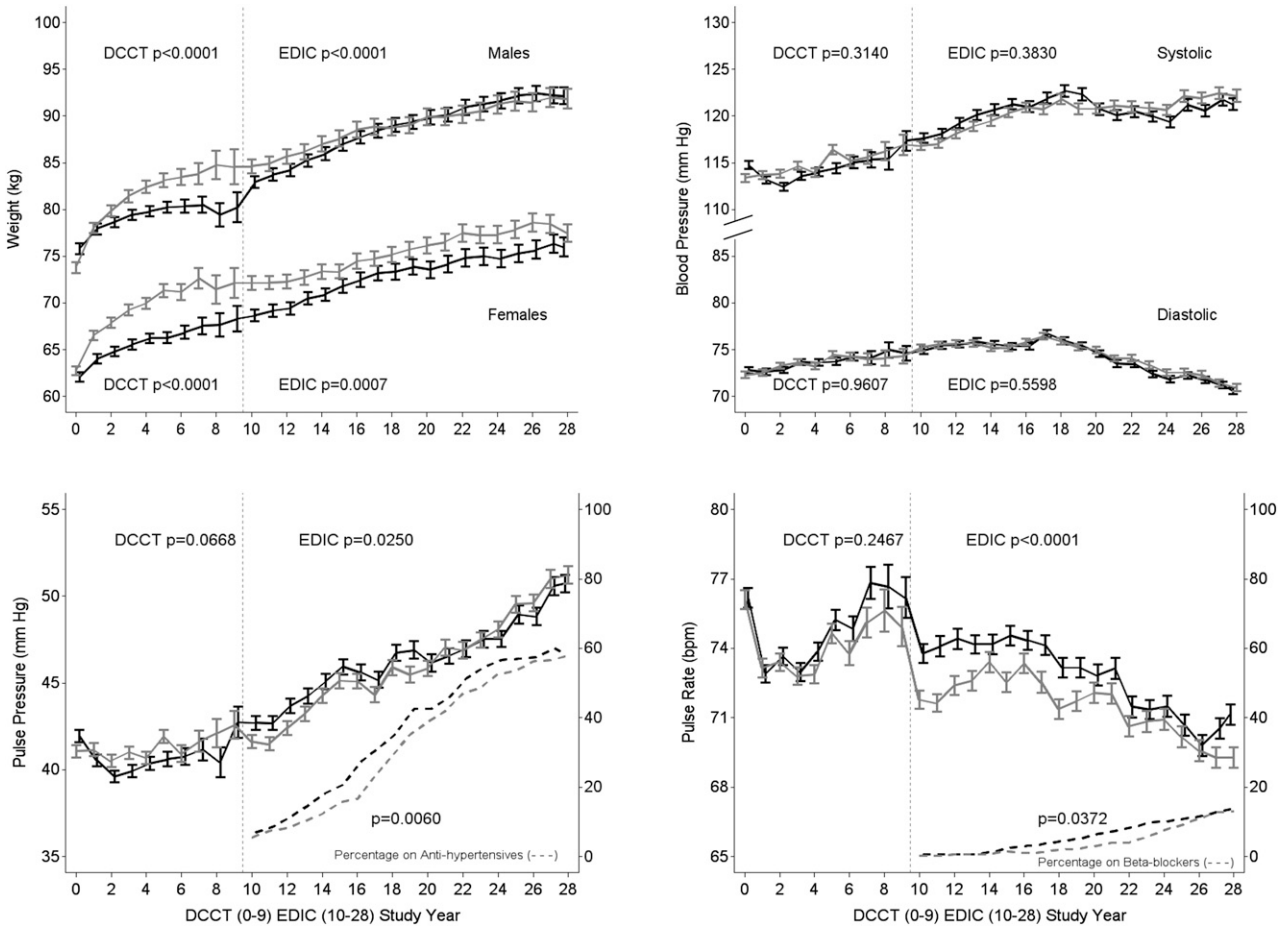

Figure 1—Body weight and hemodynamic measures during the DCCT/EDIC study by original assignment to intensive or conventional treatment during the DCCT. Data are reported as the mean ± SE at each DCCT/EDIC study follow-up year (black lines, conventional treatment; gray lines, intensive treatment). The average mean values over time are presented in Table 1. The panels for pulse pressure and pulse rate also present the proportion of subjects receiving concurrent medication.

the diastolic blood pressure rose during the first 17 years and began to fall thereafter (Fig. 1). The pulse pressure (systolic − diastolic) also increased from a mean of 42 mmHg at DCCT baseline to 52 mmHg by year 30, mainly due to the decrease in diastolic blood pressure beyond year 17 rather than to the increase in systolic blood pressure (Fig. 1). This was accompanied by an increasing prevalence of antihypertensive medication use during EDIC study (6% at year 10 to 60% by year 30). Figure 1 also shows an increasing pulse rate (after an initial dip in year 2) that persisted until year 7–8 of the DCCT, before declining during the last years of the DCCT and throughout the EDIC study. The latter may reflect the increasing use of β-blockers (1% at year 10 to 14% by year 30). Notably, a slightly higher pulse rate was observed in the conventional treatment group compared with the intensive treatment group throughout most of the DCCT/EDIC study follow-up years.

Compared with participants in the conventional group, those in the intensive treatment group had numerically lower LDL cholesterol and triglyceride levels during the DCCT (Fig. 2). The pattern became somewhat reversed during the EDIC study, although both groups experienced decreasing LDL cholesterol levels from year 12 onward as the use of lipid-lowering medication increased (2% at year 10 to 62% by year 30). Overall, serum triglyceride levels were remarkably stable throughout the DCCT/EDIC study (Fig. 2). There were no treatment group differences in HDL cholesterol levels: the levels were stable throughout the DCCT and increased by 24% by year 30 in the EDIC study (Supplementary Fig. 1).

Although the current HbA_{1c} levels in the intensive and conventional treatment groups came together at the beginning of the EDIC study follow-up period, the DCCT/EDIC study time-weighted mean HbA_{1c} values remained significantly higher in the conventional treatment group over the 20 years of the EDIC study follow-up (Fig. 2).

Association of Diabetes-Related Risk Factors With Progression of Traditional CVD Risk Factors

Table 2 presents the association of treatment group and HbA_{1c} level as a time-dependent covariate with the traditional CVD risk factors in the general population, with adjustment only for age, primary versus secondary cohort, and sex when appropriate. The regression coefficient (mean difference between groups or slope for a

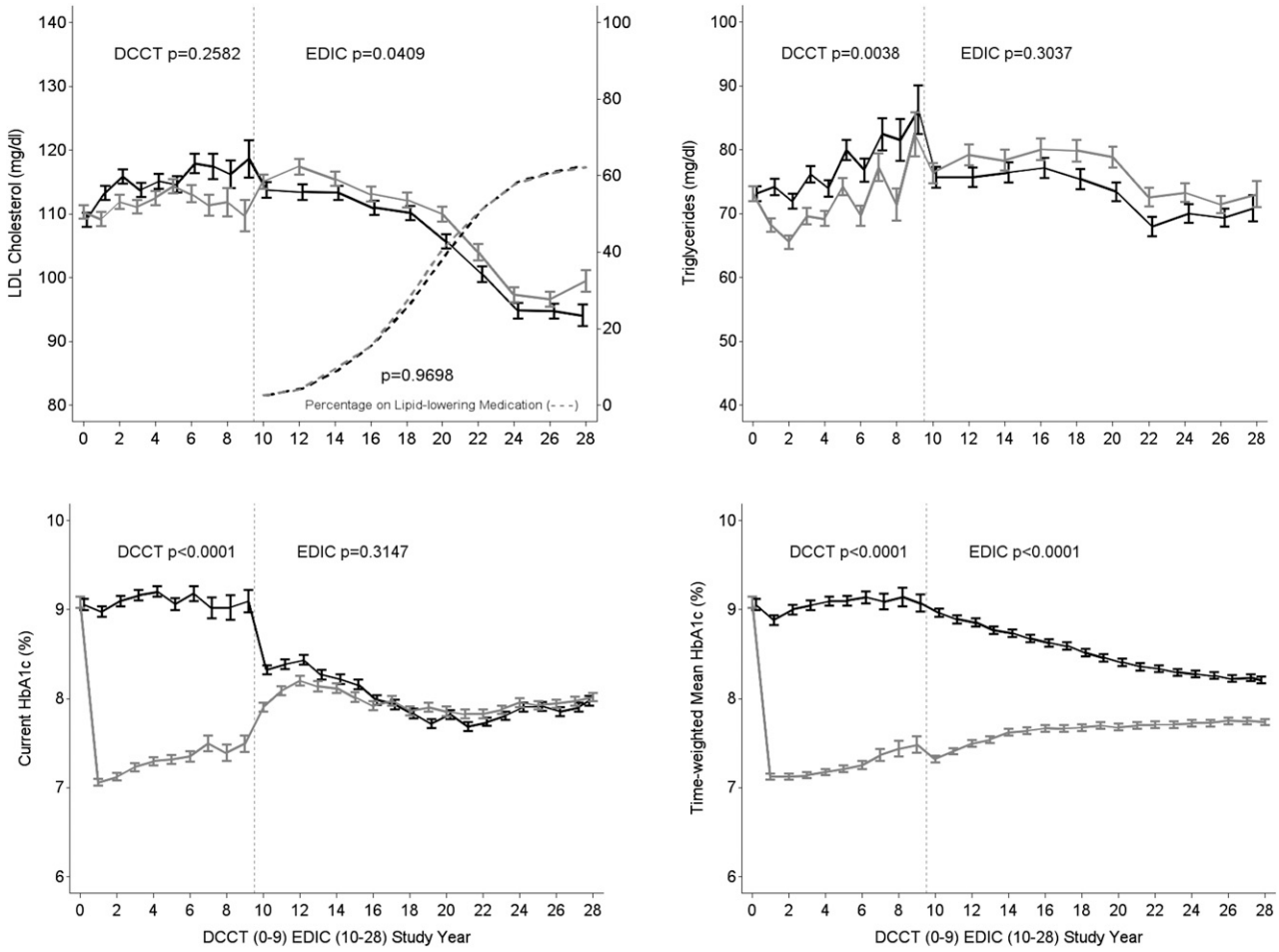

Figure 2—Lipid profile and glycemic control during the DCCT/EDIC study by original assignment to intensive or conventional treatment during the DCCT. Data are reported as the mean ± SE at each DCCT/EDIC study follow-up year (black lines, conventional treatment; gray lines, intensive treatment). The average mean values over time are presented in Table 1. The panel for LDL cholesterol also presents the proportion of subjects receiving concurrent medication. Triglyceride values were log transformed, and the geometric means are presented.

Table 2—Longitudinal association of treatment group and HbA_{1c} with traditional cardiovascular risk factors during the DCCT/EDIC study, minimally adjusted for other factors

	Traditional cardiovascular risk factors								
	BMI		Systolic BP (mmHg)	Diastolic BP (mmHg)	Pulse pressure (mmHg)	Pulse rate (bpm)	Triglycerides (mg/dL)*	HDL cholesterol (mg/dL)	LDL cholesterol (mg/dL)
	Men (kg/m^2)	Women (kg/m^2)							
Intensive vs. conventional	0.82 ± 0.12 <0.0001 (6.87)	1.30 ± 0.15 <0.0001 (8.76)	0.24 ± 0.37 0.5196 (0.64)	0.22 ± 0.25 0.3722 (0.89)	0.18 ± 0.26 0.4894 (0.69)	−0.93 ± 0.33 0.0055 (−2.78)	−6.44 ± 1.71 0.0003 (−3.64)	−0.09 ± 0.47 0.8489 (−0.19)	−1.92 ± 1.10 0.0808 (−1.75)
Current HbA_{1c} level (%)†	−0.30 ± 0.01 <0.0001 (−26.61)	−0.19 ± 0.01 <0.0001 (−14.58)	−0.38 ± 0.06 <0.0001 (−6.46)	0.18 ± 0.04 <0.0001 (4.32)	−0.48 ± 0.05 <0.0001 (−9.91)	0.31 ± 0.05 <0.0001 (6.38)	5.77 ± 0.21 <0.0001 (27.66)	0.12 ± 0.05 0.0075 (2.67)	3.36 ± 0.13 <0.0001 (26.17)
DCCT/EDIC study time-weighted HbA_{1c} level (%)†	−0.40 ± 0.02 <0.0001 (−22.02)	−0.13 ± 0.02 <0.0001 (−6.12)	−0.09 ± 0.10 0.3806 (−0.88)	0.22 ± 0.07 0.0018 (3.13)	−0.12 ± 0.08 0.1218 (−1.55)	1.17 ± 0.09 <0.0001 (13.75)	8.15 ± 0.34 <0.0001 (24.60)	−0.05 ± 0.07 0.4595 (−0.74)	3.63 ± 0.20 <0.0001 (17.99)
DCCT updated HbA_{1c} level (%)†	−0.33 ± 0.02 <0.0001 (−14.35)	−0.09 ± 0.03 0.0006 (−3.45)	−0.15 ± 0.10 0.1348 (−1.50)	0.10 ± 0.07 0.1563 (1.42)	−0.12 ± 0.08 0.1224 (−1.55)	1.02 ± 0.09 <0.0001 (11.62)	5.86 ± 0.39 <0.0001 (15.48)	−0.08 ± 0.09 0.3855 (−0.87)	2.65 ± 0.23 <0.0001 (11.41)

Each cell represents a single generalized linear mixed model adjusting for baseline age, primary prevention vs. secondary intervention group, and sex when appropriate. Data are β-estimates ± SE and *P* values (*t* statistics). β-Estimates are equal to the mean difference between groups or the slope of the association. The signed *t* statistic corresponds to the magnitude and directionality of the association. BP, blood pressure. *Triglyceride values were log transformed and the percentage change in triglyceride levels per 1-unit change in predictor is shown $[100(e^{\beta} - 1)] \pm [100(e^{\beta}*SE)]$. †Each predictor is entered into the model as a time-dependent covariate. The DCCT updated mean is defined as the cumulative glycemic exposure from baseline up to and including the HbA_{1c} level at each visit through DCCT. The DCCT/EDIC study time-weighted mean was calculated using the quarterly DCCT and annual EDIC study values weighted by 3 and 12 months, respectively.

quantitative predictor), SE, and *P* value are also shown.

Participants in the intensive treatment group had a significantly higher BMI, lower pulse rate, and lower triglyceride levels. The strongest longitudinal associations were among the lipid measurements and glycemia, with higher current HbA_{1c} levels being strongly associated with increases in triglyceride and LDL cholesterol levels. A higher current HbA_{1c} level was also associated with decreases in BMI, systolic blood pressure, and pulse pressure. Similar associations were observed for the DCCT/EDIC study time-weighted mean HbA_{1c} level as well as for the DCCT updated mean HbA_{1c} level. The magnitude and direction for each comparison in Table 2 remained the same after further adjustment for corresponding medications (e.g., antihypertensive medication for treatment of blood pressure, β-blockers for pulse rate; and lipid-lowering medications for triglyceride, and HDL and LDL cholesterol levels).

Supplementary Table 1 extends the analyses in Table 2 to include the association of all baseline and time-dependent predictors with each traditional CVD risk factor, with the signed *t* statistic to show the significance and direction of the partial association of each covariate individually (without minimal adjustments). These analyses demonstrate robust associations of numerous CVD risk factors including age, weight, smoking, physical activity, blood pressure, heart rate, and lipid values. Time-averaged triglyceride levels had a robust inverse association with HDL cholesterol levels, and positive associations with BMI, blood pressure, pulse rate, and LDL cholesterol values. Family history of hypertension was associated with blood pressure, and family history of type 2 diabetes was weakly associated with triglyceride and LDL cholesterol levels. There was no discernible association between duration of diabetes and traditional CVD risk factors, except for increased pulse pressure (secondary to a decrease in diastolic blood pressure).

Influence of Glycemia

For each significant treatment group association in Table 2, the potential mediating effect of glycemia was evaluated.

The significant treatment group differences in pulse rate and triglyceride level were attenuated after adjustment for current HbA_{1c} level (P = 0.0947 and P = 0.2876, respectively), whereas the significant association between BMI and treatment group remained largely unaffected by current HbA_{1c} values (data not shown). In additional models, the DCCT/EDIC study time-weighted and DCCT updated mean HbA_{1c} values did not mediate any of the significant treatment group associations originally observed in Table 2. As a result, current HbA_{1c} level was used in all of the subsequent multivariate models.

Multivariate Associations With Progression of Risk Factors

Supplementary Table 2 presents the association of each covariate in a multivariate model adjusted for the current HbA_{1c} level and all other factors, and Table 3 summarizes these associations for treatment group. There were no significant treatment group differences in the jointly adjusted models at the $P < 0.01$ level with the exception of BMI, which remained significantly higher in females in the intensive treatment group, even after adjusting for all other covariates (Table 3). Current HbA_{1c} level was associated with all CVD risk factors, excluding HDL cholesterol level.

Compared with the results shown in Supplementary Table 1, there were fewer significant associations shown in Supplementary Table 2 after adjustment for all other factors. Nevertheless, current HbA_{1c} level persisted as a significant predictor of the longitudinal changes in all of the CVD risk factors (with the exception of HbA_{1c} level with HDL cholesterol level). Each jointly adjusted regression model accounted for >85% of the variation in the response variables.

Longitudinal changes in male and female BMI were associated with similar risk factors, including smoking, blood pressure, and triglyceride, LDL cholesterol, and current HbA_{1c} levels (Supplementary Table 2). An increase in male BMI was also associated with older age. Not surprisingly, the systolic blood pressure was the strongest correlate of diastolic blood pressure, and diastolic blood pressure was the strongest correlate of systolic blood pressure. Systolic blood pressure and pulse pressure were both associated with gender, age,

Table 3—Longitudinal associations of treatment group and HbA_{1c} level with traditional cardiovascular risk factors during the DCCT/EDIC study, fully adjusted for all other factors

	BMI		Traditional cardiovascular risk factors						
	Men (kg/m^2)	Women (kg/m^2)	Systolic BP (mmHg)	Diastolic BP (mmHg)	Pulse pressure (mmHg)	Pulse rate (bpm)	Triglycerides (mg/dL)*	HDL cholesterol (mg/dL)	LDL cholesterol (mg/dL)
Intensive vs. conventional	−0.17 ± 0.14	1.01 ± 0.17	−0.46 ± 0.30	0.34 ± 0.19	−0.50 ± 0.29	−1.33 ± 0.51	0.03 ± 1.69	0.82 ± 0.50	1.80 ± 1.03
	0.2190	<0.0001	0.1227	0.0729	0.0872	0.0100	0.9873	0.0997	0.0820
	(−1.23)	(5.93)	(−1.54)	(1.79)	(−1.71)	(−2.58)	(0.02)	(1.65)	(1.74)
Current HbA_{1c} level (%)†	−0.35 ± 0.02	−0.25 ± 0.02	−0.37 ± 0.06	0.22 ± 0.04	−0.39 ± 0.06	0.33 ± 0.06	5.49 ± 0.23	0.02 ± 0.05	2.99 ± 0.14
	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.6538	<0.0001
	(−21.61)	(−14.43)	(−6.49)	(5.32)	(−6.62)	(5.89)	(24.77)	(0.45)	(21.04)

Each column represents a single generalized linear mixed model jointly adjusted for all other baseline and time-dependent predictors listed in Supplementary Table 2. Data are reported as β-estimates ± SE and P values (t statistics). β-Estimates are equal to the mean difference between groups or the slope of the association. The signed t statistic corresponds to the magnitude and directionality of the association. BP, blood pressure. *Triglyceride values were log transformed and the percentage change in triglycerides per 1-unit change in predictor is shown $[100(e^{\beta} - 1)] \pm [100(e^{\beta} * SE)]$. †Each predictor is entered into the model as a time-dependent covariate.

pulse rate, and current HbA_{1c} level. The longitudinal changes in HDL cholesterol level were highly influenced by behavioral factors, including smoking and drinking alcohol, whereas triglyceride and LDL cholesterol levels were associated with blood pressure, pulse rate, and HbA_{1c} level.

CONCLUSIONS

In previous reports (2,4–6), we demonstrated the beneficial effect of intensive diabetes management on atherosclerosis and the occurrence of clinical cardiovascular events among participants in the DCCT/EDIC study. These reports also demonstrated that hyperglycemia is a risk factor for CVD in individuals with type 1 diabetes. However, it is not known to what extent glycemic exposure influences the magnitude and direction of long-term changes in established CVD risk factors among patients with type 1 diabetes. The ongoing long-term follow-up of the DCCT/EDIC study cohort provides an opportunity to answer this question.

In the present report, we have examined the coprogression of CVD risk factors and their interactions with glycemic exposure among DCCT/EDIC study participants over a 30-year period of follow-up. Although age is a major risk factor for an increased risk of clinical CVD events in the general population, it was not strongly associated with increases in many risk factors in the DCCT/EDIC study cohort, with the exception of a positive association with BMI in men, systolic (but not diastolic) blood pressure, and pulse pressure. Likewise, sex was not strongly associated with lipid profile. These results suggest that the well-known influence of age and sex on clinical CVD risk in patients with type 1 diabetes is not predominantly driven by their effects on traditional risk factors. The lack of an association between the duration of diabetes and traditional CVD risk factors (notably, blood pressure and lipid levels) should be interpreted with caution, as an increasing proportion of participants received medications for the control of hypertension and dyslipidemia during the EDIC study period.

Although ambient HbA_{1c} levels in the intensive and conventional group came together at the beginning of the EDIC study follow-up period, the DCCT/EDIC study time-weighted mean HbA_{1c} values continue to be significantly higher in the conventional group. We found that the strongest longitudinal associations were among the current HbA_{1c} levels and lipid measurements, although other significant associations also emerged. The strong association among higher current HbA_{1c} levels and higher triglyceride and LDL cholesterol levels is consistent with the known effect of poorly controlled diabetes on lipid metabolism (13). Triglyceride concentration during the DCCT years, when glycemic control differed markedly between groups, was lower among subjects in the intensive treatment group, despite their higher weight gain, which reflects the impact of intensive insulin therapy and improved glycemic control in regulating triglyceride levels.

The robust association of current HbA_{1c} level with blood pressure and heart rate is concordant with known clinical associations between diabetes and hypertension, and is likely mediated by autonomic mechanisms (14,15). The pulse pressure of study participants has widened progressively (from ~40 to >50 mmHg) during the nearly 30-year follow-up period. Because a wide pulse pressure range may be a stronger predictor of heart disease than blood pressure, the latter observation is of some concern (16). The traditional etiology of elevated pulse pressure is arterial stiffness, as occurs in aging, atherosclerosis, and diabetes. In this study cohort, the increasing pulse pressure resulted from a combination of rising systolic blood pressure with relatively level diastolic blood pressure during the DCCT period to EDIC study year 17, and decreasing diastolic blood pressure with stable systolic blood pressure from EDIC study year 17 onward. Among subjects without diabetes, systolic blood pressure tends to increase progressively with age, and diastolic blood pressure also rises with age until ~60 years of age, and then decreases thereafter, most likely due to arterial stiffness and decreased vascular compliance (17). Notably, the proportion of patients receiving antihypertensive treatment increased from 6% at year 10 to 60% at year 30. The effective treatment of hypertension usually also restores pulse pressure toward more normal values. Thus, the persistent widening of the pulse pressure is not fully explained by exposure to antihypertensive agents, and could well be related to diastolic dysfunction and accelerated arterial aging associated with diabetes (17–19).

The negative association between current HbA_{1c} levels and BMI could be due to glycosuria-induced weight loss secondary to poorly controlled diabetes. Other interesting observations in the longitudinal cohort include corroboration of several physiologically congruent interactions, as follows: weight was predictive of blood pressure, heart rate, and lipid profile; smoking was associated with lower BMI, lower HDL cholesterol level, and higher heart rate, and triglyceride and LDL cholesterol levels (20–22); and physical activity was associated with lower BMI, heart rate, and triglyceride levels, and higher HDL cholesterol levels.

The present report has several strengths, including the fact that the data were obtained from a well-documented population that has been observed for 30 years. Previous reports from the DCCT/EDIC study (23) have established an association between blood pressure and AER that was significantly modified by treatment group and glycemia. The current study extends that observation by assessing the interaction of time-averaged glycemic exposure with an array of clinical, biochemical, and biobehavioral CVD risk factors. The findings indicate that these risk factors are significantly interrelated and coprogress in a time-dependent manner. The demonstration of strong longitudinal associations among HbA_{1c} level and traditional CVD risk factors argues strongly for a clinical directive to optimize control of blood pressure, dyslipidemia, and hyperglycemia in the management of patients with type 1 diabetes (24).

The DCCT/EDIC study has established that the updated weighted mean HbA_{1c} level over the DCCT and the EDIC study combined is a stronger determinant of the risk of progression of complications over time than is the current HbA_{1c} value. However, herein, the current HbA_{1c} value has a stronger association with the current value of other risk factors than does the updated mean HbA_{1c}. This indicates that the current HbA_{1c} value has a short-term association with these other risk factors. It

would also be expected that the updated mean HbA_{1c} level would have a stronger association with the updated mean of these CVD risk factors.

Among the limitations of the study, the exclusively type 1 diabetes cohort and the lack of ethnic diversity (96% non-Hispanic white) diminish the generalizability of the findings. Also, study participants had a mean BMI of $<$24 kg/m^2 at study enrollment and $\sim$27 kg/m^2 averaged over the DCCT/EDIC study period, which is not representative of the current predominantly overweight U.S. general population. Furthermore, by focusing on the interactions among glycemic and nonglycemic predictors of traditional CVD risk factors, the present report does not consider the possible contribution of nontraditional risk factors.

In conclusion, we have reported the longitudinal coprogression of glycemic and nonglycemic predictors of traditional CVD risk factors during an extensive, $\sim$30-year follow-up of the DCCT/EDIC study type 1 diabetes cohort. The interrelationships we observed among the predictors and the CVD risk factors are pathophysiologically congruent, and are in the same direction as prior observations based on the more definitive clinical CVD events. Over time, there were significant treatment group differences in a number of CVD risk factors and substantial associations with measures of HbA_{1c}. Although the significant association with current HbA_{1c} level dominated, it did not completely mediate the treatment group differences for all factors. The greater understanding of the relationships among diabetes-related risk factors and established CVD risk factors may provide insight into the design of individualized comprehensive interventions for the control of comorbidities and the reduction of CVD risk in persons with type 1 diabetes.

Appendix

Writing Group for the DCCT/EDIC Research Group. The members of the Writing Group for the DCCT/EDIC Research Group are as follows: Barbara H. Braffett, Ionut Bebu, and John M. Lachin (The Biostatistics Center, George Washington University, Rockville, MD); Samuel Dagogo-Jack (Division of Endocrinology, Diabetes and Metabolism, University of Tennessee Health Science Center, Memphis, TN); Mary Larkin (Massachusetts General Hospital Diabetes Center, Harvard Medical School, Boston, MA); William Sivitz (Department of Internal Medicine, Division of Endocrinology and Metabolism, University of Iowa, Iowa City, IA); Orville Kolterman (University of California, San Diego, La Jolla, CA); and Saul Genuth (Case-Western Reserve University, Cleveland, OH).

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Author Contributions. B.H.B. wrote the manuscript and conducted the statistical analyses. S.D.-J., M.L., W.S., I.B., O.K., S.G., and J.M.L. wrote sections of, reviewed, and edited the manuscript. B.H.B. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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