The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study at 30 Years: Overview

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OBJECTIVE

The Diabetes Control and Complications Trial (DCCT) was designed to test the glucose hypothesis and determine whether the complications of type 1 diabetes (T1DM) could be prevented or delayed. The Epidemiology of Diabetes Interventions and Complications (EDIC) observational follow-up determined the durability of the DCCT effects on the more-advanced stages of diabetes complications including cardiovascular disease (CVD).

RESEARCH DESIGN AND METHODS

The DCCT (1982–1993) was a controlled clinical trial in 1,441 subjects with T1DM comparing intensive therapy (INT), aimed at achieving levels of glycemia as close to the nondiabetic range as safely possible, with conventional therapy (CON), which aimed to maintain safe asymptomatic glucose control. INT utilized three or more daily insulin injections or insulin pump therapy guided by self-monitored glucose. EDIC (1994–present) is an observational study of the DCCT cohort.

RESULTS

The DCCT followed >99% of the cohort for a mean of 6.5 years and demonstrated a 35–76% reduction in the early stages of microvascular disease with INT, with a median HbA_{1c} of 7%, compared with CONV, with a median HbA1c of 9%. The major adverse effect of INT was a threefold increased risk of hypoglycemia, which was not associated with a decline in cognitive function or quality of life. EDIC showed a durable effect of initial assigned therapies despite a loss of the glycemic separation (metabolic memory) and demonstrated that the reduction in early-stage complications during the DCCT translated into substantial reductions in severe complications and CVD.

CONCLUSIONS

DCCT/EDIC has demonstrated the effectiveness of INT in reducing the long-term complications of T1DM and improving the prospects for a healthy life span.

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**A complete list of participants in the DCCT/EDIC Research Group can be found in N Engl J Med 2011;365:2366–2376.*

See accompanying articles, pp. 5, 8, 17, 24, 31, 39, and 44.

The plight of people with type 1 diabetes changed dramatically with the introduction of insulin therapy in 1922 (1). Type 1 diabetes was transformed from a uniformly fatal disease in the preinsulin era, with mortality occurring either acutely from diabetic ketoacidosis or subsequently from inanition owing to a chronic catabolic state, to a chronic degenerative disease. In the first 15 to 20 years of insulin therapy, a host of complications that had never been seen before was discovered in people with long-term diabetes (2). These complications, affecting the eyes, kidneys, and peripheral nervous system, were collectively called microvascular complications, to distinguish them from the less diabetes-specific but highly prevalent macrovascular disease complications. Microvascular disease and peripheral neuropathy resulted in blindness, kidney failure, and amputations (3); and macrovascular disease, exacerbated by renal dysfunction and autonomic neuropathy, increased the risk for myocardial infarctions and stroke to levels that were 10-fold or more than in the age-matched nondiabetic population (2,3).

The pathoetiology of the microvascular complications was vigorously debated during the mid-20th century (4–6). Some practitioners considered the complications a result of nonphysiologically controlled hyperglycemia; others thought that they were a glycemia-independent feature of diabetes. Perhaps the most sensible opinion regarding the role of glucose control, expressed by R.D. Lawrence, the preeminent diabetologist of his time and who had type 1 diabetes himself, was as follows: "The attempt to keep the blood sugar constantly normal may be ideal in theory, but in practice it is very difficult to achieve and makes the diabetic life unnecessarily hard without adequate benefit" (7).

The devastating consequences of the long-term complications led in part to the formation of the National Diabetes Commission by an Act of Congress (PL 93-354). In 1975, the Commission issued *The Long-Range Plan to Combat Diabetes*, which included the recommendation for the National Institutes of Health (NIH) to "initiate and support a 5-year clinical study to assess the effects of treatment of juvenile-onset diabetes on the development of microvascular and macrovascular complications."

The advances necessary to perform a definitive clinical trial were finally in place by the early 1980s. These included: the ability to manage glucose levels in the near-normal range using multiple daily injection (MDI) therapy or continuous subcutaneous insulin infusion (CSII) with external pumps, guided by self-monitoring of blood glucose (SMBG); the means of measuring chronic glycemia objectively and accurately with the glycated hemoglobin (HbA_{1c}) assay; and objective measures of long-term complications. With these tools available and with generous support from the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, which later became the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), 21 centers were selected in 1982 to plan and conduct a study that would test what had become known as the "glucose hypothesis." Practically stated, the glucose hypothesis posited that achieving near-normal glucose would ameliorate the long-term complications of diabetes. Over the course of more than a year, the investigators planned the Diabetes Control and Complications Trial (DCCT) (8). The two primary aims of the DCCT consensus protocol were to determine whether, compared with conventional therapy (CON), an intensive treatment program designed to achieve glycemic control as close to the nondiabetic range as safely possible would prevent or delay the *appearance* of early background retinopathy (primary prevention) and would prevent the *progression* of early retinopathy to more advanced forms of retinopathy (secondary intervention).

After the successful completion of a 1-year feasibility phase, during which a substantial separation of HbA_{1c} levels between the intensive therapy (INT) ("experimental") and CON ("standard") groups was achieved (9), an additional eight centers were added, and full-scale recruitment began. Recruitment ended in 1989, and the DCCT was halted by its independent oversight committee in 1993, approximately 1 year ahead of schedule, owing to the uniform and conclusive results achieved (10). The original CON group was taught INT, and the entire cohort was invited to join a long-term observational study named the Epidemiology of Diabetes Interventions and Complications (EDIC) (11). EDIC is now in its 20th year.

RESEARCH DESIGN AND METHODS

The eligibility criteria have been described in detail (8,10). Briefly, in order to address the primary prevention and secondary intervention questions, the following eligibility criteria were used: age 13–39 years with type 1 diabetes diagnosed based on clinically accepted criteria and with fasting c-peptide concentrations <0.2 nmol/L. The subjects had to be generally healthy with no history of cardiovascular disease (CVD) and without hypertension (blood pressure $<140/90$ mmHg) or dyslipidemia (8), and those with neuropathy requiring treatment were excluded. Additionally, the primary prevention cohort had to have a duration of 1–5 years with no evidence of retinopathy on fundus photography and an albumin excretion rate (AER) <40 mg per 24 h. The secondary intervention cohort could have a longer duration of diabetes (1–15 years) and had to have at least one microaneurysm in either eye. This cohort could have an AER as high as 200 mg per 24 h. Subjects in the primary prevention cohort and those in the secondary intervention cohort with <5 years duration could have 2-h stimulated c-peptide levels as high as 0.5 nmol/L; otherwise, it had to be ≤ 0.2 nmol/L.

DCCT Interventions and Metabolic Goals

The clinical goals for both treatment groups included absence of frequent symptoms of hyperglycemia or frequent or severe hypoglycemia, defined as requiring assistance from another person. DCCT INT aimed to achieve HbA_{1c} levels that were <2 SD above the mean value determined for similarly aged nondiabetic volunteers

(<6.05%, 42.6 mmol/mol). HbA_{1c} was measured monthly to aid adjustment of INT and quarterly as a process outcome in both therapy groups. Only the quarterly results were used for study data. INT was adjusted based on four or more SMBG tests with the following self-monitored glucose targets: premeals 70–120 mg/dL (3.9–6.7 mmol/L) and 2-h postmeals <180 mg/dL (10 mmol/L). In addition, a weekly 3:00 A.M. blood glucose was to be >65 mg/dL (3.6 mmol/L) in order to protect against otherwise unappreciated nocturnal hypoglycemia. To achieve the glycemic goals, participants randomly assigned to INT used at least three insulin injections per day (MDI) or CSII. The subjects and DCCT clinic staff chose which modality to use. The insulins used were those that were available at the time: clear zinc (regular) insulin for premeal boluses and in the insulin pump and NPH, lente, and beef ultralente insulin for basal delivery in MDI regimens. There was no single MDI or CSII regimen, and clinic staff and participants worked together to individualize the regimens to match lifestyle factors and achieve the SMBG and HbA_{1c} goals (12).

CON was consistent with standard care in the 1980s and usually included one or two daily injections of insulin with daily urine or SMBG. The only numeric glycemic target was if HbA_{1c} exceeded 13.5%, the mean +2 SD of the cohort's baseline value, in which case treatment was intensified independent of whether the subject had symptoms.

Outcomes

Retinopathy, which was measured objectively with stereoscopic fundus photography and graded with standardized methods by a central reading center (13), was the primary outcome used for power and sample-size calculations. Similarly important outcomes were nephropathy and retinopathy. The measurements and their frequency and definitions of outcomes are included in Table 1.

EDIC Design and Outcomes

In the wake of the successful completion of the DCCT (10), the DCCT investigators and the NIDDK decided that longer-term follow-up would provide important information regarding the durability of the original DCCT INT effects and, in particular, the effects of INT on the more-advanced stages of complications and CVD (11). After the end of the DCCT and before initiating the long-term follow-up called EDIC, all of the CON participants were offered training in INT. In addition, diabetes care was returned to the subjects' own care

Table 1—Major outcome measurements

Complication	Frequency		Defined outcomes
	DCCT	EDIC	
Retinopathy: 7-field stereoscopic and fundus photography	6 months	1/4 cohort/year, entire cohort year 4	Three-step progression*, CSME, severe NPDR, PDR
Renal function			
Albumin excretion+	Annual	Alternate years‡	Albuminuria: micro ≥40 mg/24 h, macro >300 mg/24 h
Serum creatinine (eGFR@)	Annual	Annual	eGFR: <60 mL/min/1.73 m^2
Neuropathy			
History, examination, and NCS	Baseline, year 5, and/or study end	Year 13/14	Confirmed clinical: abnormal exam and abnormal NCS or autonomic study
Autonomic			
Cardiac	Baseline, every 2 years, end	Years 13/14 and 16/17	R-R variation <15 or R-R <20 and Valsalva ratio <1.5 or orthostatic hypotension
Urologic (ED)	—	Year 10	
MNSI + monofilament	—	Annual	
Cardiovascular			
History	Annual	Annual	Aggregate major#: fatal CVD, nonfatal MI, and stroke, hospitalized
ECG	Annual	Annual	Angina, vascular procedures
Ankle-brachial index	Annual	Annual	
Carotid ultrasound	—	Years 1, 6, and 12	
CT CAC	—	Year 8	Agatston score >200
Cardiac MRI	—	Year 15	Cardiac structure, function, scars
Risk factors			
HbA_{1c}	3 months	Annual	
Fasting lipids	Annual	Alternate years‡	
Blood pressure	Annual	Annual	

*Based on modified Airlie House criteria (13); +based on a 4-h timed collection; @ calculated based on Modification of Diet in Renal Disease equation, #adjudicated by reviewers masked to treatment assignment HbA_{1c}; ‡during EDIC, albumin excretion and fasting lipids were measured in alternate years. CAC, coronary artery calcification; CSME, clinically significant macular edema; CT, computed tomography; ED, erectile dysfunction; eGFR, estimated GFR; MI, myocardial infarction; MNSI, Michigan neuropathy screening instrument; MRI, magnetic resonance imaging; NCS, nerve conduction study; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

Table 2—Clinical characteristics of DCCT/EDIC participants at DCCT baseline, DCCT closeout, and EDIC year 18

	DCCT baseline (1983–1989) (*N* = 1,441)		End of DCCT (1993) (*N* = 1,422)*		EDIC year 18 (2010–2012) (*N* = 1,284)*	
	INT	CON	INT	CON	INT	CON
n	711	730	698	717	620	597
Demographics						
Age (years)	27.2 (7.1)	26.7 (7.1)	33.6 (7.0)	33.0 (7.0)	52.3 (6.9)	51.4 (6.9)†
Female (%)	48.5	45.9	49.0	46.0	48.7	45.7
Diabetes duration (years)	5.8 (4.2)	5.5 (4.1)	12.3 (4.9)	11.9 (4.8)	30.7 (5.0)	30.2 (4.9)
DCCT primary prevention cohort (%)	49.0	51.8	49.1	51.7	47.7	50.6
Hypertension (%)||	3.1	2.1	4.4	3.9	66.6	68.8
Hyperlipidemia (%)**	22.8	23.4	25.6	29.7	68.6	68.2
Current cigarette smoking (%)	18.6	18.4	20.2	19.8	11.5	10.7
Medical treatment						
Glucose management						
Pump or multiple daily injections (≥3) (%)	0	0	97.4	5.0‡	97.6	97.7
Glucose monitoring ≥4 times a day (%)	0	0	52.7	3.8‡	67.7	70.7
Use of antihypertensive medication (%)§						
Any	—	—	—	—	60.3	62.7
ACE inhibitor or ARB	0	0	—	—	56.8	59.8
Physical examination						
BMI (kg/m^2)	23.4 (2.7)	23.5 (2.9)	26.6 (4.2)	25.0 (3.1)‡	29.1 (5.7)	28.5 (5.1)
Obese (BMI ≥30 kg/m^2) (%)	1.3	1.9	18.6	5.6‡	36.1	33.0
Systolic blood pressure (mmHg)	114.5 (11.3)	114.6 (11.4)	116.3 (11.7)	115.3 (12.0)	122.4 (15.4)	121.8 (15.1)
Diastolic blood pressure (mmHg)	73.1 (8.2)	72.9 (8.7)	74.4 (8.8)	74.3 (8.8)	71.4 (9.0)	71.3 (8.8)
Mean arterial pressure (mmHg)	86.9 (8.2)	86.8 (8.6)	88.3 (8.9)	88.0 (8.9)	88.4 (9.8)	88.2 (9.6)
Laboratory values						
HbA_{1c} (%)††	9.1 (1.6)	9.1 (1.6)	7.2 (0.9)	9.1 (1.3)‡	8.0 (1.0)	8.0 (1.0)
Plasma lipids (mg/dL)						
Total cholesterol	177.1 (32.8)	175.7 (33.6)	178.8 (31.2)	183.4 (36.6)	174.8 (35.4)	172.1 (36.4)
HDL cholesterol	50.8 (12.3)	50.3 (12.3)	50.8 (12.8)	51.5 (12.9)	61.9 (19.4)	61.5 (17.7)
LDL cholesterol	110.3 (28.7)	109.1 (29.4)	111.6 (27.2)	114.3 (31.4)	96.7 (29.2)	94.7 (29.5)
Triglycerides	80.8 (43.3)	81.8 (51.3)	82.0 (51.6)	87.8 (54.0)†	81.1 (50.6)	80.6 (71.5)
Complications						
Eye						
Retinopathy levels (%)				‡		‡
No retinopathy (10/10)	49.0	51.8	28.3	17.3	10.7	4.7
Microaneurysm only (20/≤20)	35.0	27.8	39.7	32.1	36.9	26.8
Mild NPDR (35/≤35)	11.6	15.2	21.2	28.5	21.3	18.3
Moderate NPDR (43/≤43–53/53)	4.5	5.1	8.2	14.3	16.5	19.6
Severe PDR or worse (53/<53+)	0	0.1	2.6	7.8	14.7	30.7
Renal*						
AER (%)				‡		‡
0 to <30 mg/24 h	88.3	90.0	89.8	82.2	81.5	75.1
30 to <300 mg/24 h	11.7	10.1	8.8	14.6	14.2	17.0
≥300 mg/24 h or ESRD	0	0	1.4	3.2	4.3	7.9
eGFR (mL/min/1.73 m^2)	126.0 (13.9)	126.2 (14.6)	116.0 (13.0)	117.8 (13.7)‡	93.3 (18.1)	91.7 (20.1)
Sustained eGFR <60 mL/min/1.73 m^2 (%)	0	0	0.1	0.4	3.2	5.3
Neuropathy						
Confirmed clinical neuropathy (%)	6.8	5.6	9.3	17.5‡	23.6	32.7‡

Data are mean (SD) unless otherwise indicated. *Renal measurements (AER or eGFR) were completed for 1,415 subjects at DCCT closeout and 1,217 subjects at EDIC year 17 or 18 (1,194 with AER at year 17 or 18 and 1,187 with eGFR at year 18). For EDIC year 18, clinical characteristic values were carried from measurements from the most recent visit if not measured at year 18. AER and lipid data were collected at year 17 or 18. †$P < 0.05$ by the Wilcoxon rank sum test or the χ^2 test comparing CON and INT. ‡$P < 0.01$ by the Wilcoxon rank sum test or the χ^2 test comparing CON and INT for all categories. ||Hypertension was defined by a systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or use of antihypertensive medications. ** Hyperlipidemia was defined by an LDL cholesterol level ≥130 mg/dL (3.4 mmol/L) or the use of lipid-lowering agents. ††End of DCCT HbA_{1c} values are time-averaged mean HbA_{1c} throughout the DCCT; EDIC year 17/18 HbA_{1c} values are time-averaged mean EDIC HbA_{1c}. Mean (SD) HbA_{1c} levels time-averaged through DCCT/EDIC were 7.8% (0.9%) and 8.3% (1.0%) among participants assigned to INT and CON, respectively. §Medication data were not collected during the DCCT. ACE inhibitors were prohibited during the DCCT. At EDIC year 1, ACE inhibitor use was 5.6% in the INT and 6.9% in the CON groups. ARBs were not available until later during EDIC. Antihypertensive use at EDIC year 1 was 8.7% in the INT and 10.1% in the CON groups. Primary prevention cohort = 1–5 years duration, <30 mg albuminuria per 24 h, and no retinopathy in either eye at baseline. ARB, angiotensin II receptor blocker; eGFR, estimated GFR; ESRD, end-stage renal disease; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

provider, some of whom were DCCT/EDIC investigators.

Whereas the DCCT was a controlled clinical trial, EDIC was observational. The frequency of interactions with the subjects and of the outcome measurements decreased substantially (Table 1); however, the methods of measuring glycemia, other metabolic outcomes, and complications remained identical to those used during DCCT. Several procedures were added to measure atherosclerosis (Table 1).

RESULTS

Subjects

The characteristics of the DCCT cohort at baseline and at study end, which represents the EDIC baseline, and at the most recent EDIC annual examination in 2012 are shown in Table 2. The baseline characteristics were well matched between the INT and CON for the primary prevention and secondary intervention cohorts. The changes over time largely reflect the effects of INT versus CON. Although in most long-term studies loss to follow-up may compromise the integrity and interpretation of study results, the follow-up in DCCT and subsequently in EDIC has been virtually complete. At the end of DCCT, after an average of 6.5 years (range 3–9), more than 99% (1,422 of 1,441) completed the study. After another 20 years of follow-up in EDIC, 88% of the original cohort (95% of the survivors) is being actively followed in DCCT/EDIC clinical centers.

Glycemia

The DCCT INT did not uniformly achieve the goal HbA_{1c} of $<$6.05%; however, 44% reached that level at least once during the trial (10). The median of the quarterly measured HbA_{1c} levels in INT was 7% compared with 9% in CON (Fig. 1). There was almost no crossover between INT and CON during the DCCT, other than the protocol-dictated change to INT for women assigned to CON who were planning pregnancy and during pregnancy (14). 97% of study time was spent on assigned therapy. During EDIC, the adoption of INT by the original CON group and the transition for all subjects to their own health care providers resulted in a narrowing and then disappearance of the differences in HbA_{1c} maintained during DCCT (Fig. 1).

Adverse Effects

The two major adverse events experienced by INT subjects were hypoglycemia and weight gain (15–17). The definition established for severe hypoglycemia, which has subsequently been adopted by many studies, was meant to be relatively inclusive but not to include episodes that were recognized and treated by the patients. To qualify as severe hypoglycemia, an episode had to require assistance from another and included coma or seizures or episodes requiring glucagon, IV dextrose, or oral carbohydrate administered by another person. Although the intent was to limit bias of ascertainment by collecting the hypoglycemia events at quarterly visits for both INT and CON subjects, INT subjects were seen and contacted more frequently than those in the CON group, and some of the differences in hypoglycemia may be attributable to differences in the frequency of ascertainment. The frequency of severe hypoglycemia (62/100 patient-years) and the subset of episodes involving coma or seizure (16/100 patient-years) were both threefold higher than in the CON group. Despite the increased frequency of hypoglycemia, there were no adverse effects of INT or of repeated severe episodes, on rigorously and repeatedly measured cognitive function in adults or adolescents, either during the DCCT or after even longer-term follow-up (18–20). Weight gain with INT resulted in significantly more subjects becoming overweight or obese compared with CON (17). The 4.6 kg difference in weight during the DCCT largely dissipated during the EDIC.

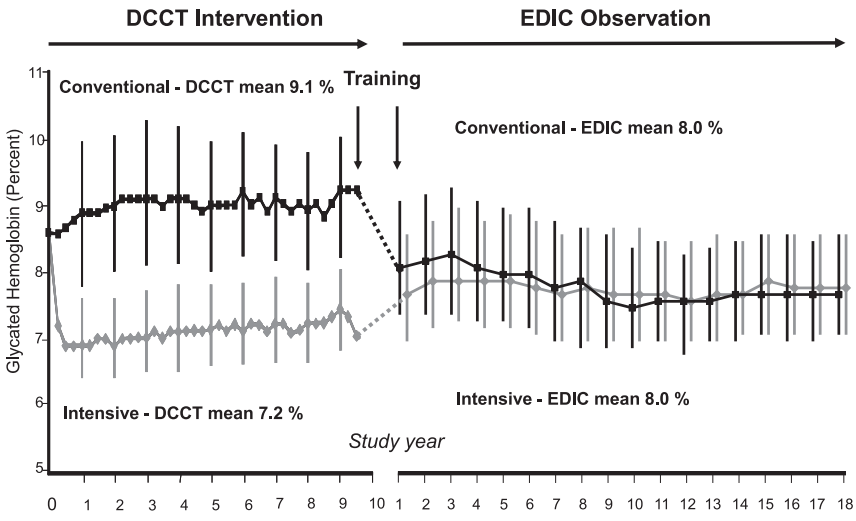

Figure 1—Median HbA_{1c} concentrations during DCCT, the "training" period between DCCT and EDIC, and EDIC. $P < 0.001$ for INT vs. CON during entire DCCT and for the first 3 years during EDIC. Reprinted and modified with permission from Nathan et al. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study at 30 years: advances and contributions. Diabetes 2013;62:3976–3986.

Outcomes

More detailed descriptions of the individual outcomes are presented in the subsequent articles in this series (21–25). In brief, DCCT INT reduced the early stages of microvascular complications by 35–76% compared with CON (Fig. 2) (10). The magnitude and consistent direction of the effects on retinopathy, neuropathy, and nephropathy led to the termination of the study 1 year ahead of schedule by the independent oversight group. Analyses of the relationship between metabolic control, measured by the "updated mean" HbA_{1c} and including approximately 18,000 HbA_{1c} measurements for each therapy group, revealed a strong association with each of the three complications (26,27). The difference in updated mean HbA_{1c} levels between the

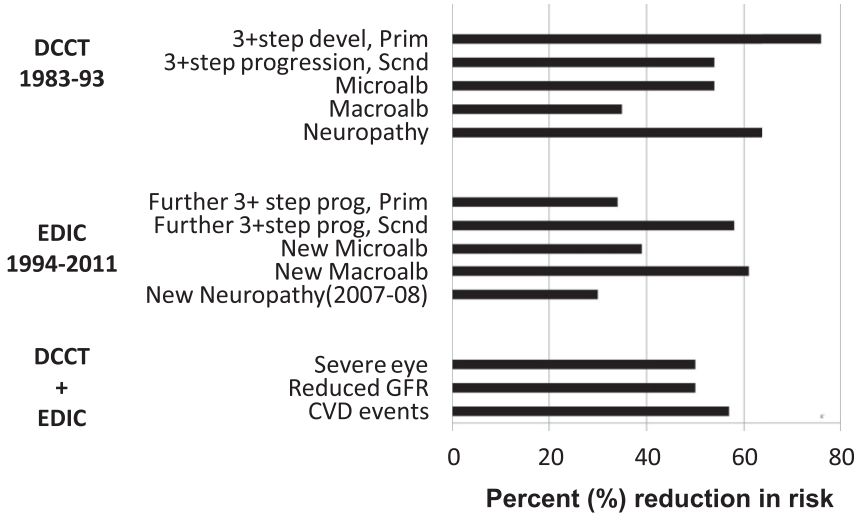

Figure 2—Summary of reduction in major complications with INT compared with CON during DCCT, EDIC, and combined study periods. 3+step devel, Prim: three-step or more development of retinopathy based on Early Treatment of Diabetic Retinopathy scale (ref. 13) in the primary prevention group. Scnd: secondary intervention group. Microalb: microalbuminuria defined as albumin excretion ≥40 mg/24 h. Macroalb: macroalbuminuria defined as albumin excretion >300 mg/24 h. Reduced GFR: estimated GFR <60 mL/min/1.73 m^2. CVD events: CVD including myocardial infarctions, stroke, and CVD death. Reprinted with permission from Nathan et al. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study at 30 years: advances and contributions. Diabetes 2013;62:3976–3986.

therapy groups explained the vast majority (>98%) of the difference in complications between the groups (26), leaving little room for other established or putative risk factors to play a role in the trial's differential outcomes.

EDIC/Metabolic Memory

Considering the powerful effect that glycemic separation had on the outcomes during DCCT, the subsequent narrowing and then disappearance of the difference in HbA_{1c} levels between the two original therapy groups during EDIC could logically have been expected to result in the subsequent parallel development of complications. However, the first 4 years of the EDIC follow-up demonstrated a further widening of the differences in outcomes, after adjusting for EDIC baseline outcomes (28). This phenomenon of a durable effect on complications of prior metabolic control was named "metabolic memory." It affects all of the microvascular complications (29–32). Studies during EDIC suggested that glycation of long-lived proteins, such as dermal collagen, might account for this persistent effect (33). Regardless of the mechanism, metabolic memory has lasted for at least 10 years.

The long-term EDIC follow-up has allowed the study of the impact of INT versus CON on more advanced complications than were studied during the DCCT. Major beneficial effects of INT on advanced complications (34), including retinopathy (35), nephropathy (reduced glomerular filtration rate [GFR]) (36), and autonomic manifestations of neuropathy (37), have been demonstrated (Fig. 2). Finally, measurements of atherosclerosis in several macrovascular beds, including carotid intima media thickness (38) and computed tomography–measured coronary artery calcification (39), have revealed less atherosclerosis in the INT group. The clinical expression of these changes, fatal and nonfatal myocardial infarctions and stroke, were also reduced by INT, with a 58% reduction in CVD events after a mean of 18 years of follow-up from the beginning of the DCCT (40).

CONCLUSIONS

The DCCT and its observational EDIC follow-up were designed to determine whether the long-term complications that affect people with type 1 diabetes could be ameliorated by intensive glycemic therapy. The DCCT/EDIC convincingly demonstrated that the glucose hypothesis was correct and that an intervention that aimed to achieve glycemia as close to the nondiabetic range as safely possible reduced all of the microvascular and cardiovascular complications of diabetes. Translating the findings of the DCCT/EDIC into clinical care has substantially improved the long-term health of people with type 1 diabetes.

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