The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study at 30 Years: Summary and Future Directions

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OBJECTIVE

The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study continues to address knowledge gaps in our understanding of type 1 diabetes and the effects of intensive therapy on its long-term complications.

RESEARCH DESIGN AND METHODS

During the DCCT (1982–1993), a controlled clinical trial of 1,441 subjects with type 1 diabetes, and the EDIC (1994–present), an observational study of the DCCT cohort, core data collection has included medical history questionnaires, surveillance health exams, and frequent laboratory and other evaluations for microvascular and macrovascular disease. Numerous collaborations have expanded the outcome data with more detailed investigations of cardiovascular disease, cognitive function, neuropathy, genetics, and potential biological pathways involved in the development of complications.

RESULTS

The longitudinal follow-up of the DCCT/EDIC cohort provides the opportunity to continue monitoring the durability of intensive treatment as well as to address lingering questions in type 1 diabetes research. Future planned analyses will address the onset and progression of microvascular triopathy, evidence-based screening for retinopathy and nephropathy, effects of glycemic variability and nonglycemic risk factors on outcomes, long-term impact of intensive therapy on cognitive decline, and health economics. Three new proposed investigations include an examination of residual C-peptide secretion and its impact, prevalence of hearing impairment, and evaluation of gastrointestinal dysfunction.

CONCLUSIONS

With the comprehensive data collection and the remarkable participant retention over 30 years, the DCCT/EDIC continues as an irreplaceable resource for understanding type 1 diabetes and its long-term complications.

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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, 9, 17, 24, 31, and 39.

The closing article in the series celebrating the 30th anniversary of Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study reflects on how past investigations have shaped the study's future directions. The preceding articles on retinopathy, nephropathy, neuropathy, and cardiovascular disease have provided detailed updates on the state of the complications of diabetes in the cohort over the past 30 years. Collectively, the message is clear: chronic glycemia is the major modifiable factor driving the development and progression of the complications of type 1 diabetes (1–6). With intensive management of their diabetes, patients can achieve lower glycemia and reduce the risk of developing complications, including severe disease (7). In turn, patients free of complications report a good and sustained diabetes-related quality of life (8). The substantial effects of intensive therapy on primary prevention during DCCT, compounded by metabolic memory established during EDIC, make it imperative to intervene with intensive therapy as early after diagnosis as possible to effectively slow the course of complications.

As we move forward, the durability of our intervention will continue to be monitored: Will the effects of intensive therapy—metabolic memory—decrease over time? EDIC will continue to monitor the trajectory of the development and progression of microvascular and cardiovascular disease. DCCT/EDIC core studies have been the foundation for many collaborations, each initiative advancing our understanding of the multisystem effects of diabetes and guiding future clinical and basic science investigations (Fig. 1). In this spirit, several new ancillary studies are planned to investigate clinical topics across diverse fields, such as residual β-cell function, hearing dysfunction, and gastric disturbances.

RESEARCH DESIGN AND METHODS

Participant Retention

As reviewed previously, the DCCT interventional study was conducted between 1982–1993, and since 1994 EDIC has continued as an observational follow-up of the consenting DCCT participants, comprising 95% of the surviving members of the original DCCT cohort (9,10). Retention during EDIC has been consistent (93–96%) whether considering original recruitment into primary prevention or secondary intervention groups or random assignment to intensive or conventional treatment. DCCT/EDIC ancillary studies are offered to all subjects, and compliance has routinely been >90% for studies involving minor procedures and/or questionnaires. Even with procedure-intensive ancillary studies, such as the cardiac magnetic resonance imaging (MRI), participation rates were 81% or better (11).

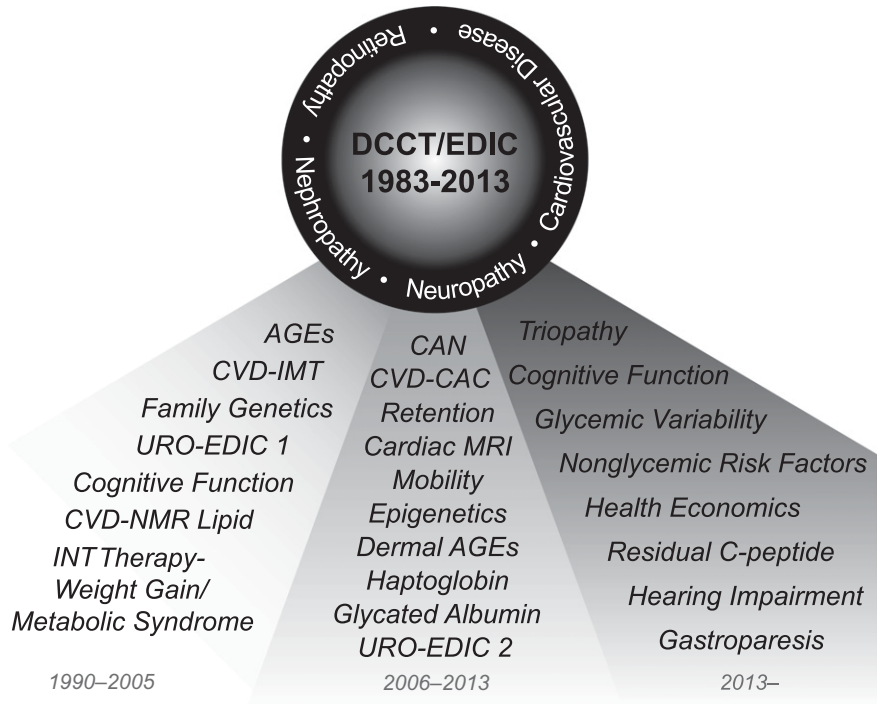

Figure 1—The DCCT/EDIC core investigations have been the center of a diverse array of supplemental studies and collaborations over the past 30 years. The black circle denotes the major outcomes (i.e., retinopathy, nephropathy, neuropathy, and cardiovascular disease) studied during the DCCT (1983–1993) and throughout EDIC (1994–present). Extending from these core investigations, a multitude of supplemental studies have been performed, starting from 1990–2005, the late DCCT/early EDIC period; continuing with 2006–2013, the first EDIC extension period; and expanding to 2013–forward, the current extension of EDIC. Family genetics study, first-degree relative genetic studies (12); CVD-CAC, coronary calcium CT scan (13); CVD-NMR lipid, lipid studies (14); URO-EDIC 1, study of urological dysfunction (15); CVD-IMT, carotid ultrasounds (16–18); AGEs, advanced glycation end products (19); cognitive function, neurocognition testing (20–22); CAN, cardiac autonomic neuropathy testing (23); cardiac MRI, enhanced cardiac MRI (11); dermal AGEs, dermal advanced glycation end product study (24,25); retention, participant retention study (26); glycated albumin measurements (27,28); haptoglobin levels (29); cardiovascular biomarkers; epigenetics; mobility, joint mobility; and URO-EDIC 2, repeat study of urological dysfunction.

Current Study Design and Core Outcomes

For each DCCT/EDIC participant, the current core protocol is performed on an annual basis and includes the major data collection form that reviews the participants' health history by system and updates intercurrent events; denotes critical diabetes-related health information including all treatments and hypoglycemia severity, awareness, and frequency during the prior 3 months; and records the results of the standardized annual physical examination focusing on diabetes complications—yearly HbA_{1c} and electrocardiogram, fasting lipid profiles every other year, urine albumin-to-creatinine ratio every other year, and ophthalmologist exam and fundus photographs once every 4 years. Core data collection of HbA_{1c}, fasting lipids, and renal collections has exceeded 89%, 90%, and 91%, respectively, on an annual basis.

Additional Study Outcomes

In addition to the core data collection, the breadth of DCCT/EDIC investigations has been increased through supplemental studies proposed by the DCCT/EDIC Study Group and collaborations with experts in various fields of diabetes research (Fig. 1). These studies are typically performed at the time of an annual visit. Data from the supplemental studies and collaborations have been incorporated into the longitudinal dataset and will be used in the planned analyses. This includes data from the following studies: first-degree relative genetic studies (12), coronary calcium computed tomography scan (13), lipid studies (14), urological dysfunction (URO-EDIC 1) (15), carotid ultrasounds (16–18), advanced glycation end products (AGEs) (19), neurocognition testing (20–22), peripheral nerve conduction testing (5,20–22), cardiac autonomic neuropathy testing (23), enhanced cardiac MRI (11), dermal AGE study (24,25), participant retention study (26), glycated albumin measurements (27,28), and haptoglobin levels (29). More recent supplemental studies with ongoing analyses include cardiovascular biomarkers, epigenetics, joint mobility, and repeat of urological dysfunction (URO-EDIC 2).

RESULTS

Metabolic Memory

As presented in the earlier accompanying manuscripts, the data through EDIC year 18 suggest that the beneficial risk reductions afforded by intensive relative to conventional therapy, while persistent and significant, are decreasing over time (30–33). Declining risk reductions are evident across microvascular complications: risk reduction for further progression of retinopathy falling from 70% to 53% to 46% at EDIC year 4, year 10, and year 18, respectively; risk reduction for confirmed clinical neuropathy decreased from 64% at DCCT closeout to 30% at EDIC year 14; and risk reduction for albuminuria with intensive therapy dropping from a high of nearly 60% at EDIC year 8 to nearly 40% at EDIC year 18, which is identical to the risk reduction seen at DCCT closeout. The fall in relative benefit of intensive therapy is almost certainly due to the adoption of intensive therapy by the original conventional therapy group and the waning of metabolic memory over time. The relative contribution of DCCT HbA_{1c}, which is also declining in the case of retinopathy, to these risk reductions over time has important clinical as well as biological implications. The underlying mechanistic link(s) between hyperglycemia and the development of complications in various organ systems remains a critical unanswered question. The potential mechanisms for the lasting effects of metabolic memory may involve genetic factors, epigenetic changes, and/or glycation of proteins, all of which have been and continue to be explored in DCCT/EDIC. The DCCT/EDIC family genetic study has identified several loci that regulate risk of developing retinopathy (34), nephropathy (35,36), and erectile dysfunction (37). Initial epigenetic investigations were presented during the 2013 American Diabetes Association Scientific Sessions and suggest intriguing links between glycemia-associated histone acetylation and activation of recognized pathogenic inflammatory cascades. In previous DCCT/EDIC publications, AGEs have been shown to correlate with the presence of microvascular complications at DCCT closeout and to predict the development and progression of complications in EDIC, all independent of the HbA_{1c} (19,38). The potential genetic factors predisposing to accelerated AGE formation are currently under investigation.

Core Initiatives

The 30-year longitudinal data collected and the remarkable retention of our research participants provide an invaluable diabetes resource, and the DCCT/EDIC and its collaborators hope to address several novel questions in diabetes care in the next few years.

- Defining the relative time course of the development of retinopathy, nephropathy, and neuropathy ("triopathy") to answer such clinical questions as: "Can the rate of progression of retinopathy predict individuals that will progress to more advanced renal disease?" and "What is the frequency of triopathy and what are the dominant risk factors?"
- Establishing the evidence-based frequency of screening of retinopathy and nephropathy
- Refining our prior 7-point self-monitoring of blood glucose data to investigate the role of glycemic variability on outcomes as well as perform a current cross-sectional examination of glycemic variability using continuous glucose monitoring
- Exploring the contributions of nonglycemic risk factors to risk reduction for macrovascular as well as microvascular outcomes
- Monitoring for effects of glycemic control on neurocognition: Will the rate of age-related cognitive decline in our cohort be different when compared with the general population?
- Continuing to monitor the bottom line—that intensive diabetes management prevents costly complications and is economically sage

Ancillary Initiatives

Building on these core initiatives, additional ancillary studies are planned. First, prior DCCT data demonstrated that intensive therapy preserved insulin

secretion, measured as C-peptide (39). Those with preserved C-peptide secretion had lower HbA_{1c} with less frequent hypoglycemia and reduced development of retinopathy and nephropathy. Now, in EDIC year 20, the following questions are posed.

- Using modern, ultrasensitive assays, is there residual β-cell function after an average diabetes duration of 30 years?
- What factors influence residual β-cell function?
- What is the physiologic significance of low levels of C-peptide?
- Will there remain a beneficial reduction in rates of complications associated with preserved insulin secretion?

Based on pilot data obtained with 4-h mixed-meal tolerance tests on 58 DCCT/EDIC subjects, mixed-meal tolerance tests are planned for the entire EDIC cohort. Three different ultrasensitive C-peptide assays will be used to provide comparative analyses of detection limits. The C-peptide results, in combination with the extensive, historical database, will extend our understanding of the relationship of long-term C-peptide production with HbA_{1c} levels over time, insulin dose requirements, hypoglycemia rates, and complications. Of importance, the study will also seek to identify the factors that mediate β-cell preservation and provide hope for future treatment options for type 1 diabetes.

A second initiative stems from the observation that hearing impairment is more common in type 2 diabetes than in the nondiabetic population (40,41). Early detection of hearing loss allows for earlier intervention, which preserves quality of life. The current proposal includes standardized hearing tests at all EDIC centers with oversight by a centralized audiology unit. The DCCT/EDIC participants' nondiabetic partners/spouses will be used as control subjects. The prevalence of hearing impairment in type 1 diabetes, its potential correlation with other microvascular complications, and the relationship with glycemia and other risk factors will be investigated.

Third, abnormal gastric emptying is a manifestation of autonomic neuropathy that challenges many patients' daily routine and their glycemic control. This initiative aims to advance our understanding of the prevalence of gastroparesis, symptomatic and asymptomatic as well as delayed and rapid types. In addition to symptom-related questionnaires, participants will complete the validated stable isotope ^{13}C-Spirulina platensis gastric emptying breath test (42). Like the C-peptide study, a pilot investigation with 80 participants across seven EDIC centers is currently in progress.

CONCLUSIONS

The DCCT/EDIC set the standard of care for clinical management of type 1 diabetes, which has forever changed the course of its complications. Intensive diabetes management remains the primary approach to prevent or slow the progression of complications. Now entering the fourth decade of study, the DCCT/EDIC core objectives continue to emphasize the rigorous assessment of microvascular and cardiovascular disease and traditional and novel risk factors. The comprehensive, longitudinal data collection and continued successful collaboration between the DCCT/EDIC investigators and research partners should provide answers to questions that will guide the clinical care of type 1 diabetes. The improvement in the long-term prospects for people with type 1 diabetes brought about through DCCT/EDIC should continue with these efforts.

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