Celebrating 30 Years of Research Accomplishments of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study

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The landmark Diabetes Control and Complications Trial (DCCT) and its follow-up study, the Epidemiology of Diabetes Interventions and Complications (EDIC), have changed the way that type 1 diabetes is treated, and have led to improvements in the health and quality of life of people with the disease. In this Perspective, we look back at the 30 years since the start of DCCT to celebrate the scientific achievements of the DCCT/EDIC study group and patient volunteers—achievements that have had far-reaching benefits for type 1 diabetes and beyond. The insights that continue to emerge from DCCT/EDIC underscore the importance of supporting long-term research on chronic diseases such as type 1 diabetes. We also describe factors that contributed to the success of DCCT/EDIC, its public health implications, and how results continue to inform current-day research directions supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH). A complementary Perspective from the DCCT/EDIC investigators summarizes the methods, and results, and clinical implications of these seminal studies (1).

A UNIQUE TIME TO ANSWER AN IMPORTANT QUESTION ABOUT TYPE 1 DIABETES MANAGEMENT

In the late 1970s to the early 1980s, there was considerable debate about whether the potential benefits of intensive glycemic control in reducing the development of diabetes complications outweighed the risks of hypoglycemia (2–4). The studies done before the DCCT were small and short in duration and had enrolled subjects with preexisting retinopathy, thus failing to resolve the controversy about the risks and benefits of intensive treatment or to address primary prevention. Moreover, some studies in individuals with established eye disease showed an early worsening of retinopathy with intensive blood glucose control (5–7). Delineation of the natural history of the preproliferative phases of diabetic retinopathy in conventionally treated type 1 diabetes and validation of retinal photography as an outcome measure provided the tools needed to design a clinical trial of the effects of an intervention on diabetic retinopathy. At the same time, there was significant progress in developing new tools and tests needed for intensive glycemic control, such as meters for self-monitoring of blood glucose, multiple daily injection regimens, insulin pumps, and the hemoglobin A_{1c} (HbA_{1c}) assay. Therefore, the confluence of key scientific questions, along with new tools and techniques that would permit testing of those questions, set the stage for beginning a rigorous trial to examine the safety and efficacy of intensive glycemic control to slow development of diabetes complications.

Such a trial was recommended by the National Commission on Diabetes. The Commission was established by the National Diabetes Mellitus Research and Education Act (Public Law 93–354), which was signed into law in 1974. The government was uniquely positioned to support this type of trial: It would not have been conducted by industry because it tested an approach to treatment rather than a specific drug or agent. Therefore, after obtaining input from an external panel of scientific experts, the NIDDK solicited research applications in 1981 to begin the DCCT.

The DCCT began in 1983 with a vanguard study of safety and feasibility and expanded in 1986 to a full trial conducted at 29 centers in the U.S. and Canada. The trial compared the effects of intensive versus conventional treatment of blood glucose levels on the development of retinopathy and other vascular complications. It enrolled 1,441 people aged 13–39 years with type 1 diabetes. Half had diabetes duration 1–5 years, no preexisting retinopathy, and urinary albumin excretion of <40 mg/24 h (primary prevention cohort) and half had diabetes duration 1–15 years, very mild to moderate nonproliferative retinopathy, and urinary albumin excretion of <200 mg/24 h (secondary intervention cohort). Participants in the intensive treatment group kept their blood glucose and HbA_{1c} levels as close to normal as safely possible through a regimen that included frequent self-monitoring of blood glucose and at least three insulin injections per day or use of an insulin pump. Conventional treatment consisted of one or two insulin injections per day, with once-a-day urine or blood glucose testing. The two treatment groups achieved markedly different average HbA_{1c} levels: 9% and 7% on average for the conventional and intensive groups, respectively. Completed a year early in 1993 due to the magnitude of the difference in key outcomes, the DCCT proved conclusively that intensive therapy reduced the risk of retinopathy and other microvascular complications by 35–76% in the primary and secondary cohorts combined compared with what was then conventional treatment (8).

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THE IMPORTANCE OF LONG-TERM RESEARCH

The numerous insights that have emerged from the follow-up EDIC study, which began in 1994, underscore the importance of the long-term support of research on chronic diseases. In particular, an important unanswered question after the DCCT ended was the effect of glucose control on cardiovascular disease (CVD), as the number of CVD cases was fewer but not statistically significantly different in the intensive versus the conventional groups at the end of the trial (9). That question was answered in 2005—over 20 years from the start of the trial—when DCCT/EDIC researchers reported that intensive glycemic control reduced the risk of nonfatal heart attack, stroke, or death from cardiovascular causes by 57% (10). These results are particularly significant because people with type 1 diabetes face a 10-fold increased risk of CVD death compared with the general age-matched population (11,12).

EDIC also found that the finite period of intensive glucose control, averaging 6.5 years during DCCT, yielded a "metabolic memory." That is, the reduced risk for complications carried forward during EDIC, although HbA_{1c} levels converged to about 8% in both the former intensive and conventional groups soon after the transition to EDIC (13). This finding was subsequently confirmed for type 2 diabetes in the UK Prospective Diabetes Study (UKPDS) and called the "legacy effect" (14). EDIC is providing novel information on the durability of metabolic memory, with more recent results showing that the differences in new cases of retinopathy between participants who received the intensive treatment and those who received conventional treatment are beginning to narrow (15). Nonetheless, prevalence of retinopathy and other vascular complications remains substantially different between the groups three decades after the start of DCCT, suggesting that patients implement intensive glucose control as early in the course of the disease as safely possible.

The DCCT established the efficacy of intensive therapy in reducing the development of albuminuria, a biomarker for kidney damage identified around the time the study began (16). In 2011, after an average 22-year follow-up, EDIC demonstrated that early intensive therapy not only continued to reduce albuminuria, but also decreased participants' long-term risk of developing clinically significant kidney dysfunction by 50% (17). The validation of biomarkers such as albuminuria as predictors of clinically significant microvascular disease was a key prerequisite for conduct of the DCCT. The lack of similarly well-validated biomarkers predictive of CVD in type 1 diabetes and the expense and duration of trials statistically powered to detect group differences in CVD events has limited our ability to test therapeutic approaches to reduce CVD risk in type 1 diabetes. Because the DCCT/EDIC has obtained several surrogate measures of CVD—including magnetic resonance imaging of the heart, cardiac computed tomography of coronary calcification, and ultrasonography of carotid intimal media thickness—continued long-term follow-up of participants as more CVD events occur may allow their validation as surrogate measures of CVD risk, and thus make feasible the use of clinical trials to examine efficacy of statins and other therapies in reducing CVD in type 1 diabetes.

The ability to follow patients over time has also provided an opportunity to look at outcomes not anticipated when the trial was designed, and to examine them from both an intention-to-treat and observational perspective. For example, UroEDIC has examined urologic and sexual function (18–20). Researchers have also examined the interplay of complications, reporting the effects of autonomic neuropathy on cardiac function (21,22) and analyzing renal effects on CVD. Other recently completed or planned studies are examining the effects of type 1 diabetes and its therapy on disorders of aging such as cheiroarthropathy, hearing loss, and cognitive impairment.

EDIC has also allowed the research group to examine the long-term safety of the intensive therapy intervention. Although intensive therapy increased severe hypoglycemia threefold in the DCCT (8), after an average of 18 years of follow-up there was no difference in cognitive function between treatment groups in the entire study population (23) or in the adolescent participants (24). However, since the DCCT did not enroll patients younger than 13 years old, an important unanswered research question is the safety of intensive treatment in younger children. Intensive treatment caused excess weight gain in the DCCT, which persisted in the EDIC and was associated with CVD risk factors, including central obesity, insulin resistance, higher blood pressure, and less favorable lipid levels (25). Further follow-up will determine whether these changes mitigate the long-term benefit of intensive treatment on CVD events.

BENEFITS FOR TYPE 1 DIABETES AND BEYOND

Findings from the DCCT/EDIC have transformed the management of type 1 diabetes and stimulated the development of subsequent trials assessing the role of glycemic control in type 2 diabetes. These trials have informed clinical guidelines developed by the American Diabetes Association (ADA) and other groups (26). However, when the ADA recommended HbA_{1c} of 7% as a general treatment goal for most patients with diabetes soon after the DCCT, the lack of standardization of HbA_{1c} assays made it difficult to use these targets in clinical practice. Therefore, the NIDDK and the Centers for Disease Control and Prevention (CDC) sponsored the National Glycohemoglobin Standardization Program (NGSP), led by DCCT investigators, to standardize clinical laboratory HbA_{1c} measurement to that of the DCCT/EDIC. Subsequently, variability of HbA_{1c} results among clinical laboratories has been steadily reduced, as the NGSP has tightened certification requirements (27). The availability of a standardized test has allowed international experts to recommend HbA_{1c} as a more convenient diagnostic test for type 2 diabetes (28). The DCCT also spurred the creation of the National Diabetes Education Program (NDEP), co-led by the NIDDK and the CDC, to disseminate the findings to the public (www.ndep.nih.gov) and stimulated multifaceted research efforts to develop tools and therapies that aid patients in achieving glycemic targets.

The DCCT established the value of HbA_{1c} not only as a measure of disease management, but also as a surrogate outcome for future clinical trials in both type 1 and type 2 diabetes. HbA_{1c} remains the primary efficacy end point for antihyperglycemic drug approval. Use of this surrogate outcome dramatically shortened the cost and duration of efficacy trials of new therapies and was the basis for the U.S. Food and Drug Administration approval of approximately 10 new classes of drugs for type 2 diabetes.

The DCCT found that intensive therapy early after diagnosis helped sustain endogenous insulin secretion, which, in turn, was associated with better metabolic control and lower risk for hypoglycemia and chronic complications

(29). This finding not only underscored the importance of initiating intensive diabetes management as early as safely possible after type 1 diabetes is diagnosed, but also led a group of international experts convened by the ADA to conclude that assessment of β-cell function, as measured by C-peptide levels, is the most suitable primary outcome for pivotal intervention studies of therapies aimed at preservation of β-cell function in patients with type 1 diabetes (30). Stimulated C-peptide has been the primary outcome for numerous studies of potential therapies to preserve β-cell function in patients with type 1 diabetes conducted by the Type 1 Diabetes TrialNet, the Immune Tolerance Network, and industry.

PARTNERING FOR SUCCESS

While NIDDK takes great pride in its role as the lead sponsor of the DCCT/EDIC, we are grateful for partnerships with scientific experts, other NIH components, and industry that have been vital to the study's success. The DCCT/EDIC study group has continually reached out to and been enriched by new expertise that has fostered application of cutting-edge technology to participant assessment. For example, collaborations with genetics experts led to the discovery of a gene region near the *SORCS1* gene associated with HbA_{1c} levels (31). Most recently, collaboration with a small business to test a device measuring skin-intrinsic fluorescence showed that this measurement correlated strongly with average HbA_{1c} over time, age, smoking, and kidney damage, making it a potentially useful marker of diabetes complications (32). Other collaborators have been instrumental in contributing to CVD imaging studies, comprehensive neuropathy and neurocognitive evaluations, epigenetics studies to elucidate an understanding of metabolic memory, and research on urologic complications.

Because diabetes complications are relevant to multiple components of the NIH, other NIH Institutes and Centers have played important roles, including the National Eye Institute through support of diabetic retinopathy studies; the National Heart, Lung, and Blood Institute through support of studies on surrogate measures for CVD; and the National Institute of Neurological Disorders and Stroke through support of neuropathy studies. General Clinical Research Centers/Clinical and Translational Science Awards funded by the National Center for Research Resources/National Center for Advancing Translational Sciences have provided clinic space and support at DCCT/EDIC sites. Furthermore, industry partners have provided funding and in-kind donations such as insulin and glucose monitors, which have been critical for leveraging federal support.

The DCCT/EDIC is an exceptional research resource and NIDDK is committed to assuring that maximum research value is obtained from this landmark study. Therefore, DCCT/EDIC data and study biosamples are publicly available through the NIDDK Central Repositories (www.niddkrepository.org) and several funding opportunity announcements have encouraged the broader research community to propose studies using these resources.

DCCT/EDIC PARTICIPANTS: 30 YEARS OF EXTRAORDINARY DEDICATION

In looking back over the past 30 years, it is clear that a major reason for the success of DCCT/EDIC is the extraordinary dedication of the patient volunteers. To date, 95% of living DCCT participants continue to participate in EDIC, and a remarkable 93% participated in every annual visit during EDIC's first 15 years. What are the reasons behind the long-standing dedication? Participants' survey results showed that the opportunity to be involved in cutting-edge research is the key reason for their interest in continuing in the study, closely followed by a desire to help others (33).

Contributing to patient loyalty is the high priority that the DCCT/EDIC research team has placed on patient well-being and safety. For example, during DCCT, women in the conventional group who were pregnant or planning a pregnancy received intensive therapy out of concern for the health of the mother and child (8). Indeed, subsequent research showed that tight control of glucose beginning before conception lowers the risk of birth defects, miscarriage, and newborn death to a range that is close to that of the general population (34). Subsequently, with financial resources provided by NIDDK, the research team taught participants in the conventional group how to implement intensive therapy, so that the patients could benefit as soon as possible after the DCCT results were known and be among the first, other than the intensive group, to implement intensive therapy in the U.S. Continued support and access to study personnel and cutting-edge scientific information has been a hallmark of the study. Investigators apprised participants of major DCCT findings before they were made public, and continue to provide the participants with practical, useful, and current information through the twice-yearly *EDIC Gazette*, produced by EDIC study cochair Dr. Saul Genuth and study coordinators, with submissions by study participants. For DCCT/EDIC's 30th anniversary, a commemorative booklet celebrating the participants' huge contribution to diabetes research and their extraordinary dedication is being distributed to the participants. Participants residing in and near Chicago also attended the DCCT/EDIC symposium at the 73rd Scientific Sessions of the ADA and received a standing ovation for their loyalty and altruism.

The exceptional efforts of the DCCT/EDIC study coordinators, many of whom have been with the study since its inception, have contributed immeasurably to the extraordinary participant retention. The study coordinators were empowered as partners in planning and developing DCCT, which was unusual during that time period, and their role has evolved over time to include chairing study committees and serving as co-investigators of several ancillary studies. In 2011, the NIDDK convened study coordinators from multiple NIH-supported type 1 diabetes studies to discuss insights and best practices. The DCCT/EDIC coordinators shared how they have addressed challenges over the years, by developing flexible scheduling, maintaining strong participant–staff bonds, creating a DCCT/EDIC community, and assuring patients they could always "come home" to the study whenever they wanted (35).

DCCT/EDIC: SHAPING PUBLIC HEALTH AND CURRENT RESEARCH DIRECTIONS

The outlook for people with long-standing type 1 diabetes has greatly improved due to better understanding of the importance of intensive glucose control as established by the DCCT/EDIC, as well as to advances in insulin formulations, insulin delivery, glucose monitoring, and the treatment of CVD risk factors (36). Life expectancy of those with type 1 diabetes has increased by 15 years when comparing people diagnosed in 1950–1964 with those diagnosed in 1965–1980 (37). That good news must be weighed against the fact that type 1 diabetes is a difficult disease to manage. Even the highly dedicated DCCT/EDIC

patients—who were selected for their ability to adhere to the intervention—have been unable to achieve or maintain the level of control during EDIC that the intensive group achieved during DCCT (13,15).

Certain populations are particularly vulnerable. The DCCT showed that the adolescents enrolled in the trial—both in the intensive and conventional arms—did not achieve as good glucose control as the adults (38). This finding was prescient, and has subsequently been validated in other studies examining glucose control in adolescents or young adults (39–42). Because DCCT/EDIC showed that early glycemic control is so important, the finding that adolescents are not achieving recommended levels of glycemic control has led NIDDK to intensify research efforts on that age-group to improve adherence to medications and medical regimens. Those affected by poverty also face major challenges implementing the findings from the DCCT/EDIC. The situation is particularly dire in undeveloped, resource-poor countries, but also affects people living in the U.S. For example, research has shown a link between socioeconomic status and type 1 diabetes outcomes in the U.S., with lower education associated with higher rates of end-stage renal disease and coronary artery disease, and lower income associated with higher rates of autonomic neuropathy and lower-extremity arterial disease (43). Research from the SEARCH for Diabetes in Youth Study has also shown racial/ethnic and socioeconomic disparities related to type 1 diabetes management in American youth (44,45). These findings inform public health and research efforts to ensure that all people with type 1 diabetes—in the U.S. and worldwide—benefit from what we have learned from the DCCT/EDIC.

The enduring and compelling benefits of early intensive glycemic control of type 1 diabetes demonstrated in the DCCT/EDIC lend urgency to research to develop tools to make such control achievable and less burdensome. Our Beta Cell Biology Consortium and other projects are pursuing strategies to develop β-cell replacement or regeneration approaches. We are also devoting considerable resources to the development of technologies, such as the artificial pancreas, to help patients achieve recommended levels of glycemic control with lower risk of hypoglycemia, and we are gratified by the rapid progress in this area. The support of behavioral research will continue to be important as these new tools are developed. Finding ways to help patients of all ages live better with type 1 diabetes and use current and emerging technologies safely and effectively will remain a high priority for NIDDK-supported research and help us realize the full benefits of DCCT/EDIC.

While glycemic exposure is the dominant risk factor, other factors may also contribute to the risk of type 1 diabetes complications (46–49). Combined analysis of DCCT/EDIC and other well-characterized cohorts may elucidate genetic and other risk factors for complications that could inform personalized medicine as well as identify novel therapeutic targets. Moreover, the molecular mechanisms underlying the metabolic memory of past glucose levels remain to be elucidated. Identifying the cellular or epigenetic basis of metabolic memory could suggest therapeutic approaches to mimic or induce the protective effects of good glucose control, foster repair or regeneration of affected tissues, or obviate detrimental changes associated with early sustained hyperglycemia. Our diabetes research strategic plan (50) addresses a number of questions related to metabolic memory including how a finite period of near-normal or poor blood glucose control can have such long-lasting effects, and whether there is a point in the development of complications in which the progression becomes relatively independent of blood glucose control.

CONCLUSIONS

This Perspective describes only a small part of the accomplishments of the DCCT/EDIC research team and patient volunteers over the past 30 years and of the far-reaching impact of their achievements, which have transformed diabetes care worldwide and continue to shape NIDDK's research directions. The NIDDK applauds the skill and dedication of the scientists, study coordinators, and patient volunteers of the DCCT/EDIC study. They are a key reason why people with type 1 diabetes are living longer, healthier lives than ever before—what a remarkable legacy.

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