Diabetes Clinical Trials: What Is New at NIDDK?

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Controlled, randomized clinical trials are the foundation on which the American Diabetes Association (ADA) and other groups develop guidelines for diabetes care. The Diabetes Control and Complications Trial (DCCT)[1] provided definitive evidence that intensive glycemic control dramatically reduces the microvascular complications of type 1 diabetes. The United Kingdom Prospective Diabetes Study[2] provided similar findings for type 2 diabetes. The results of these trials formed the basis for ADA's current standards of care and led the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the Centers for Disease Control and Prevention (CDC) to create the National Diabetes Education Program (NDEP) to disseminate the new guidelines to providers and patients.[3]

As additional clinical trials demonstrated the importance of blood pressure and LDL cholesterol control in preventing vascular complications of diabetes, the NDEP expanded its focus to the "ABCs of diabetes": **A**1C, **B**lood pressure, and **C**holesterol. More recently, the Diabetes Prevention Program demonstrated that a 5–7% weight loss and modest physical activity (30 minutes a day, 5 days a week) reduced the development of type 2 diabetes by 58% over 2.8 years.[4] In response, the NDEP launched its "Small Steps. Big Rewards. Prevent Type 2 Diabetes." campaign, providing patients and providers with tools for lifestyle change. Additional information about this program is available at the NDEP Web site (www.ndep.nih.gov).

There are often significant differences between trials supported by industry and those supported with public funds. The nature of the intervention under study is one consideration. It is noteworthy that the seminal DCCT did not focus on specific medications and thus would not have been undertaken by industry. Another consideration is the size of the group affected by a disease. While there is a large and unfortunately rapidly expanding market for type 2 diabetes therapies, the prevalence of type 1 diabetes makes it a less attractive target for commercial therapeutic development, despite its devastating consequences for individuals affected. A special appropriation has led to a major expansion of publicly funded research focused on the prevention, treatment, and cure of type 1 diabetes. More information about this appropriation of $150 million annually through 2008 can be found through the NIDDK Web site (http://www.niddk. nih.gov/fund/diabetesspecialfunds).

Many clinicians can recall that, just over a decade ago, we did not know if it was worth the cost and the risk of hypoglycemia to intensively control glucose. Now, tight glucose control is a standard of care. The Epidemiology of Diabetes and Its Complications study continues to follow the DCCT patients and has found that the benefits of early intensive management grow ever greater over time.[5] Further, by establishing hemoglobin A_{1c} (A1C) as a valid surrogate outcome for trials of new therapeutics, the DCCT paved the way for multiple industry-supported trials that led to the approval of new classes of diabetes medicines.

Today, a new generation of publicly funded diabetes trials is addressing key questions about diabetes therapy, and other clinical research efforts are underway to identify new therapeutic targets. This brief review highlights some of the ongoing efforts at NIDDK that have the potential to shape future diabetes care, with an emphasis on those that provide opportunities for patient participation and provider referral.

Testing Approaches to Prevent or Slow Type 1 Diabetes: Type 1 Diabetes TrialNet

Several clinical studies have demonstrated that we can estimate specific levels of increased risk for type 1 diabetes in relatives of those with type 1 diabetes.[6] Moreover, β-cell function can be assessed in new-onset diabetes. Preservation of β-cell function is associated with improved control of diabetes and thus may reduce the risk of diabetes complications.[7] These observations form the basis for efforts to undertake a systematic series of clinical trials to prevent progression to type 1 diabetes in family members of those with type 1 diabetes and to preserve β-cell function in patients with new-onset type 1 diabetes and residual β-cell function.

To capitalize on the research opportunities presented by this knowledge, the National Institutes of Health (NIH) has created an international network of cooperative clinical groups, the Type 1 Diabetes TrialNet (http://www.diabetes-trialnet.org) and a complementary effort, the Immune Tolerance Network (ITN; http://www.immunetolerance.org/public). These collaborative networks

provide state-of-the-art methods for measuring immune parameters. They also provide the infrastructure to conduct clinical trials of new prevention-oriented strategies in those at risk for diabetes and trials to test strategies to preserve β-cell function in patients with new-onset type 1 diabetes.

TrialNet builds on the findings of the Diabetes Prevention Trial-Type 1 (DPT-1),[8] which demonstrated that large preventive trials of type 1 diabetes are feasible in family members of those with type 1 diabetes. While insulin administration was not found to be effective in preventing type 1 diabetes in this trial, the DPT-1 did validate current predictive tools (HLA and autoantibodies) for identifying individuals at risk for the disease and thus paved the way for future trials. TrialNet and ITN will facilitate rapid, preliminary testing of emerging therapeutic strategies. Those that prove most promising in small studies aimed at preserving β-cell function in patients with new-onset diabetes can then be moved quickly into larger-scale prevention trials.

A natural history study recently initiated by TrialNet will assess risk in family members of individuals with type 1 diabetes and develop information on disease progression. This study will also identify subjects eligible for future prevention studies and information useful for prevention protocol design. TrialNet is also recruiting subjects to investigate the efficacy of mycophenolate mofetil and daclizumab in maintaining pancreatic β-cell function in recently diagnosed type 1 diabetes. TrialNet is collaborating with ITN in further study of anti-CD3 [hOKT3g1(Ala-Ala)], a drug being developed that showed promising results in a phase 1 study in patients with new-onset type 1 diabetes.[9]

Islet Transplantation for Type 1 Diabetes

Recently, there has been significant progress toward islet transplantation as a therapy for type 1 diabetes. The success of the Edmonton Protocol[10] has established islet transplantation as a viable therapy for patients whose disease cannot be effectively managed with current methods of exogenous insulin administration. However, serious obstacles remain for development of islet transplantation as a cure for type 1 diabetes, most notably the toxicity associated with current regimens of immunosuppression and islet administration and the limited supply of human cadaveric islets, which is sufficient for only a small fraction of the people who could potentially benefit from this therapy.

NIH is pursuing multiple initiatives directed at developing methods to attain an unlimited supply of islets for transplantation, improving methods for isolating islets and administering transplanted islets, and developing approaches to minimize the toxicity of immunotherapy required for transplantation. Of particular note is a new cooperative clinical islet transplantation consortium to be established this autumn to develop and implement research protocols addressing obstacles that must be overcome for islet transplantation to reach its full potential as a cure for type 1 diabetes.

Clinical Networks Uncovering New Targets for Type 1 Diabetes Therapy

In type 1 diabetes, unknown environmental factors combine with genetic susceptibility to destroy the insulin-producing β-cells. Two recently launched clinical research networks are undertaking ambitious efforts to elucidate the genetic and environmental factors giving rise to type 1 diabetes.

The Type 1 Diabetes Genetics Consortium (T1DGC; http://www.t1dgc.org) will organize international efforts to identify genes that determine an individual's risk of type 1 diabetes. Progress towards this goal worldwide has been limited by a lack of sufficient clinical and genetic resources. The T1DGC is seeking to identify 2,500 new families with two or more siblings with type 1 diabetes to achieve sufficient sample size and sample availability for gene identification.

The Environmental Determinants of Diabetes in the Young is a multi-center, multinational epidemiological study of neonates at high genetic risk. High-risk neonates in three regions of the United States and three European countries will be followed until adolescence for identification of infectious agents, dietary factors, or other environmental exposures that may contribute to the initiation of autoimmunity and type 1 diabetes.

Type 2 Diabetes in Children

Once considered a disease of adults, type 2 diabetes has emerged as an increasing problem in pediatric diabetes clinics, particularly those serving disadvantaged and minority populations. To examine the incidence and prevalence of all forms of diabetes among children and adolescents in the United States, the CDC and NIH have launched SEARCH for Diabetes in Youth (http://www.cdc.gov/diabetes/pubs/factsheets/search.htm), a six-region study covering 5 million youth, or 6% of U.S. children under age 20.

To explore approaches to treatment of type 2 diabetes in youth, the NIDDK recently launched TODAY (**T**reatment **O**ptions for Type 2 **D**iabetes in **A**dolescents and **Y**outh; www.TODAYstudy.org). Researchers plan to enroll 750 children and teens aged 10–17 years who have been diagnosed with type 2 diabetes in the past 2 years. Participants will be assigned in equal numbers to each of three treatment groups: metformin alone, metformin and rosiglitazone in combination, and metformin plus intensive lifestyle change aimed at losing weight and increasing physical activity. The TODAY study's main goal is to determine how well and for how long each treatment approach controls blood glucose levels. The effects of the treatments on insulin production, insulin resistance, body composition, quality of life, safety, and cost-effectiveness will also be assessed.

A related multi-center trial will address prevention of risk factors for type 2 diabetes in middle school–aged children. Currently, investigators are

pilot-testing components of the study, which will include: *1*) in-school environmental change aimed at enhancing the physical education curriculum and increasing physical activity; *2*) in-school environmental change aimed at changing school food services; *3*) a social marketing campaign to promote changes in physical activity and nutrition; and *4*) a computer-based individually tailored health curriculum.

Reducing the Burden of Cardiovascular Disease in Diabetes

Cardiovascular disease (CVD) accounts for two-thirds of deaths in individuals with diabetes, and the risk of CVD is increased two- to fourfold in those with diabetes compared to the general population.[11] With the growing prevalence of obesity in the United States, CVD associated with type 2 diabetes is expected to become an even greater public health challenge. While randomized clinical trials have demonstrated that control of certain risk factors can substantially reduce the burden of CVD in diabetes, major unanswered questions about optimal management of type 2 diabetes with respect to CVD are being addressed in ongoing clinical trials jointly sponsored by the NIDDK and the National Heart, Lung, and Blood Institute (NHLBI).

Although weight loss and increased physical activity can dramatically reduce the development of type 2 diabetes in those at high risk, a benefit of weight loss in preventing complications in people with diabetes has not yet been established through clinical trials. It is important to establish the benefits and cost-effectiveness of weight loss in people with type 2 diabetes to inform decisions regarding use of scarce health care resources. To address this issue, NIH is conducting the largest clinical trial to date to examine the long-term health effects of voluntary weight loss. The Look AHEAD (Action for Health in Diabetes) trial[12] is a multi-center, randomized clinical trial that will examine the consequences of a lifestyle intervention designed to achieve and maintain weight loss over the long term through decreased caloric intake and increased exercise.

Look AHEAD just completed enrollment of 5,000 obese patients ages 55–75 with type 2 diabetes. Participants were randomly assigned to one of two interventions: Lifestyle Intervention or Diabetes Support and Education. The trial will compare the effects of the two interventions on major cardiovascular events: heart attack, stroke, and cardiovascular-related death. Look AHEAD patients will be followed for up to 11.5 years. In addition to CVD outcomes and risk factors, health-related quality of life, general health, and the cost and cost-effectiveness of Lifestyle Intervention relative to Diabetes Support and Education will be assessed.

The NHLBI-led Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial is designed to test the effects on major CVD events of *1*) intensive glycemia control (A1C target < 6.0% vs. 7.0–7.9%); *2*) fibrate treatment to increase HDL cholesterol and lower triglycerides (in the context of good LDL cholesterol and glycemic control); and *3*) intensive blood pressure control (systolic blood pressure target of < 120 mmHg vs. < 140 mmHg in the context of good glycemic control). All 10,000 middle-aged or older participants with type 2 diabetes will be in the glycemia trial. In addition, one 2×2 trial will also address the lipid question in 5,800 of the participants and the other 2×2 trial will address the blood pressure question in 4,200 of the participants. Recruitment is ongoing (http://www.accordtrial.org/public/index.cfm).

The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial[13] (http://www.bari2d.org) addresses two questions about therapy in adults with type 2 diabetes and stable coronary artery disease (CAD) who might be candidates for revascularization. One randomization in the 2×2 design will examine the effect on progression of CAD of treatment to attenuate insulin resisitance compared to insulin-providing treatment targeted to the same level of glycemic control. The other randomization will compare aggressive medical management and the revascularization procedure of physician/patient choice to aggressive medical management alone to determine if early revascularization reduces mortality and cardiac events in individuals with type 2 diabetes and mild, stable angina or with at least 50% luminal diameter narrowing. Patients with unstable angina or coronary anatomy requiring intervention are not eligible. Recruitment is ongoing for this challenging NHLBI-led study, which aims to enroll 2,800 subjects.

The Road Forward: Addressing Important Remaining Questions

In 1999, the congressionally established Diabetes Research Working Group (DRWG) issued its recommendations for NIH support of diabetes research over the subsequent 5 years. The DRWG emphasized the opportunities for addressing clinical research questions. It noted that, compared to other common diseases that dramatically affect public health, such as hypertension and CVD, relatively few trials had been carried out in diabetes.

Since the DRWG report was issued, several important trials have been completed, and there has been substantial progress in expanding both the number of clinical trials and the infrastructure to conduct clinical research in diabetes. Studies are underway to explore novel strategies for diabetes prevention, to define the treatment strategies that will reduce the risk of CVD, and to define optimal therapy for the emerging problem of type 2 diabetes in children.

Thus, we can anticipate a further expansion of knowledge that will further improve therapy for people with or at risk for diabetes. Moreover, new understandings of the immunopathogenesis of type 1 diabetes, insulin action and the biology of insulin-responsive tissues, and β-cell development and function will yield new targets for therapy. A key challenge will be translation of this new

knowledge from the bench to the bedside.

The increased prevalence of overweight and obesity is driving the epidemic of type 2 diabetes in America. Information about the pathophysiology and natural history of obesity is necessary to address this major new threat to public health. We must identify factors that confer resistance in a lucky few to an environment that predisposes most Americans to weight gain. We must also identify particular factors, such as puberty or middle age, associated with weight gain and patterns of weight gain associated with diabetes. Strategies to prevent weight gain and maintain weight loss, particularly low-cost ways to influence behavior, are critically important. These should be assessed in coordinated studies in which approaches can be evaluated with common endpoints.

Finally, we must ensure that the American people benefit from our research effort and that evidence-based medicine from clinical trials is rapidly yet rigorously translated into clinical practice across various models of health care delivery. To this end, NIDDK is supporting diabetes prevention and control projects, and science-based approaches to modify patient and provider behavior and enhance delivery of effective diabetes care.

REFERENCES

[1]The DCCT Research Group: The effect of intensive diabetes treatment on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:978–986, 1993

[2]The UKPDS Study Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:837–853, 1998

[3]Clark CM, Fradkin JE, Hiss RG, Lorenz RA, Vinicor F, Warren-Boulton E: Promoting early diagnosis and treatment of type 2 diabetes: the National Diabetes Education Program. *JAMA* 284:363–365, 2000

[4]The DPP Research Group: Reduction in incidence of type 2 diabetes with life-style intervention or metformin. *N Engl J Med* 346:393–403, 2002

[5]Writing Team for the DCCT/EDIC Research Group: Sustained effect of intensive treatment of type 1 diabetes mellitus on development and progression of diabetic nephropathy: the Epidemiology of Diabetes Interventions and Complications (EDIC) study. *JAMA* 290:2159–2167, 2003

[6]Devendra D, Liu E, Eisenbarth GS: Type 1 diabetes: recent developments. *BMJ* 328 (7442):750–754, 2004

[7]Palmer JP, Fleming GA, Greenbaum CJ, Herold KC, Jansa LD, Kolb H, Lachin JM, Polonsky KS, Pozzilli P, Skyler JS, Steffes MW: C-peptide is the appropriate outcome measure for type 1 diabetes clinical trials to preserve beta-cell function: report of an ADA workshop, 21–22 October 2001. *Diabetes* 53:250–264, 2004

[8]Diabetes Prevention Trial–Type 1 Diabetes Study Group: Effects of insulin in relatives of patients with type 1 diabetes mellitus. *N Engl J Med* 346:1685–1691, 2002

[9]Herold KC, Hagopian W, Auger JA, Poumian-Ruiz E, Taylor L, Donaldson D, Gitelman SE, Harlan DM, Xu D, Zivin RA, Bluestone JA: Anti-CD3 monoclonal antibody in new-onset type 1A diabetes mellitus. *N Engl J Med* 346:1692–1698, 2002

[10]Shapiro AM, Lakey JR, Ryan EA, Korbutt GS, Toth E, Warnock GL, Kneteman NM, Rajotte RV: Islet transplantation in seven patients with type 1A diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. *N Engl J Med* 343:230–238, 2000

[11]National Institute of Diabetes and Digestive and Kidney Diseases: National diabetes statistics fact sheet: general information and national estimates on diabetes in the United States, 2003. Bethesda, Md., U.S. Department of Health and Human Services, National Institutes of Health, 2003. Available online at http://diabetes.niddk.nih.gov/dm/pubs/statistics/index.htm#17

[12]Ryan DH, Espeland MA, Foster GD, Haffner SM, Hubbard VS, Johnson KC, Kahn SE, Knowler WC, Yanovski SZ, the Look AHEAD Research Group: Look AHEAD (Action for Health in Diabetes): design and methods for a clinical trial of weight loss for the prevention of cardiovascular disease in type 2 diabetes. *Control Clin Trials* 24:610–628, 2003

[13]Sobel BE, Frye R, Detre KM, the Bypass Angioplasty Revascularization Investigation 2 Diabetes Trial Group: Burgeoning dilemmas in the management of diabetes and cardiovascular disease: rationale for the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) Trial. *Circulation* 107:636–642, 2003

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