ABCs of Diabetes Research

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Research studies are continually conducted to improve knowledge in the area of prevention and treatment of disease entities. The field of diabetes is no exception. Each year, hundreds of studies are performed to improve our understanding of diabetes and its complications. Because study titles are often lengthy and cumbersome, acronyms are often used to quickly refer to a given trial. Investigators and sponsors strive to come up with catchy acronyms to appropriately describe their trials while making them easy to remember. These acronyms make up the ABCs of diabetes research (Table 1).

This article describes several major trials in diabetes research and gives a brief overview of a few of the recent trials. Specifically, it focuses on trials that deal with prevention of diabetes, identification and treatment of cardiovascular disease in those with diabetes, genetic linkages, and the treatment of diabetes.

Prevention

Multiple clinical trials have been aimed at preventing the onset of diabetes. Among these are the DPT-1, ENDIT, DPP, XENDOS, STOP NIDDM, HOPE, and DREAM.

The DPT-1 (**D**iabetes **P**revention **T**rial in Type **1** Diabetes),[1] sponsored by the National Institutes of Health (NIH), the American Diabetes Association (ADA), and the Juvenile Diabetes Research Foundation (JDRF), was designed to determine whether type 1 diabetes can be prevented. Both genetic and environmental factors contribute to increased risk of developing type 1 diabetes. Relatives of patients with type 1 diabetes have a 10- to 20-fold increased risk of developing diabetes compared to those without a family history. This trial tested two hypotheses—specifically, that diabetes could be prevented with either low-dose insulin injections or oral insulin.

The study set out to screen and identify those relatives at high risk for developing diabetes. Screening included measuring immune markers in the blood, such as antibodies against insulin, islet cells, or the enzyme glutamic acid decarboxylase (GAD), which are present in most people who develop type 1 diabetes. In addition, HLA typing was performed, and first-phase insulin response was measured. Those at high risk were entered into one of two phases: an oral insulin trial or a low-dose injection trial.[1]

The results of the phase in which participants received low-dose insulin injections were announced at the 61st ADA Scientific Sessions in Philadelphia, Pa., in June 2001. The investigators reported that low-dose insulin injections did not prevent type 1 diabetes in those with impaired glucose secretion and a >50% risk of developing diabetes based on initial screening data. Although the study failed to prevent type 1 diabetes, these results greatly improve our understanding of how to predict diabetes risk and which events lead to the development of diabetes.

IN BRIEF

This article describes the major studies in the field of diabetes, which are most commonly known by their acronyms. Studies dealing with prevention, cardiovascular disease in diabetes, genetic linkages, and treatment are highlighted. Descriptions of study design, outcomes when available, and funding sources are provided. Information is also provided about participating in upcoming studies.

The second phase of the study, which focuses on the potential use of oral insulin in preventing type 1 diabetes, is ongoing. Participants in that phase are randomized to either oral insulin or placebo and followed every 6 months to determine the presence of type 1 diabetes. Because the body responds differently to oral medications than to injections, it is possible that oral therapy could work even though insulin injections did not. The effects will depend on the digestive immune system recognizing insulin in a unique way and developing a response that delays the progression of diabetes or prevents its occurrence.

More information about the DPT-1 and recruiting sites can be found by calling 1-800-HALT-DM1 (1-800-425-8361) or visiting the Website http://www.niddk.nih.gov/patient/dpt_1.htm.

The ENDIT (**E**uropean **N**icotinamide **D**iabetes **I**ntervention **T**rial),[1] sponsored by JDRF, is another trial investigating treatments that may prevent type 1 diabetes. This prospective study of 552 first-degree relatives of people with type 1 diabetes will address whether nicotinamide can reduce the rate of type 1 diabetes in this group. Results

Table 1. Acronyms in Diabetes Research

Research Studies
Diabetes Prevention Trial Type 1 Diabetes (DPT-1)
European Nicotinamide Diabetes Intervention Trial (ENDIT)
Diabetes Prevention Program (DPP)
Xenical in the Prevention of Diabetes in Obese Subjects (XENDOS)
Heart Outcomes Protection Evaluation (HOPE)
Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medications (DREAM)
Study to Prevent Non-Insulin Dependent Diabetes Mellitus (STOP NIDDM)
Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes (BARI 2D)
Action to Control Cardiovascular Risk in Diabetes (ACCORD)
Detection of Ischemia in Asymptomatic Diabetics (DIAD)
Look Action for Health in Diabetes (Look AHEAD)
Genetics of Coronary Artery Disease in Alaskan Natives (GOCADAN)
Genetics of Kidney in Diabetics (GoKinD)
Nutrition, Exercise, Weight Loss, Diabetes and You (NEW DAY)

Research Sponsors
National Institutes of Health (NIH)
National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
National Heart, Lung, and Blood Institute (NHLBI)
National Institute of Nursing Research (NINR)
Office of Research on Minority Health (ORMH)
Office of Research on Women's Health (ORWH)
American Diabetes Association (ADA)
Juvenile Diabetes Research Foundation (JDRF)

are expected to be reported sometime in 2003.

Unlike DPT-1 and ENDIT, the DPP (**D**iabetes **P**revention **P**rogram) was a multicenter clinical trial that sought to determine whether type 2 diabetes could be prevented in a group of people at high risk for developing the disease. The study was sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases in cooperation with numerous other agencies, organizations, and pharmaceutical companies. More than 3,200 volunteers with impaired glucose tolerance (IGT), a condition that precedes the diagnosis of type 2 diabetes, were randomly assigned to one of three treatment groups: *1*) lifestyle intervention, *2*) metformin (Glucophage) therapy, or *3*) placebo.[2]

The lifestyle intervention group had the goal of reducing body weight by 7% through a modified diet and increased physical activity to 150 min/week. The medication group received metformin, 850 mg twice daily, and was given standard lifestyle information on nutrition and exercise. The placebo group also received information on standard lifestyle changes.[3] A fourth group, treated initially with troglitizone (Rezulin) was discontinued in June 1998 because of that drug's potential liver toxicity.

The DPP results were announced at the Diabetes Mellitus Interagency Coordinating Committee Scientific Presentation in August 2001, about a year earlier than originally anticipated. The results provided overwhelming evidence that diabetes could be prevented or delayed. The lifestyle intervention group showed a 58% reduction in the occurrence of diabetes compared to the placebo group. The lifestyle group achieved and maintained an average weight loss of 5% and 150 min/week of exercise, most commonly walking. The metformin group had a 31% reduction in the occurrence of diabetes as compared to the placebo group. It is anticipated that participants will continue to be followed to determine whether the cardiovascular complications associated with diabetes are also improved by these two forms of therapy.

Other trials are also investigating treatments for preventing type 2 diabetes. The XENDOS trial (**XEN**ical in the Prevention of **D**iabetes in **O**bese **S**ubjects)[4] is an ongoing trial of 3,305 participants to investigate if orlistat (Xenical) combined with a low-calorie diet and exercise can reduce the incidence of type 2 diabetes in obese subjects. This study, sponsored by Hoffman LaRoche, Inc., recruited its participants over a 4-month period. With the results of the DPP and other prevention trials[5] showing favorable results from weight loss, clinicians look forward to announcement of the XENDOS results.

Other investigators have attempted to find treatments to prevent type 2 diabetes by looking retrospectively at data from large clinical trials. The HOPE (**H**eart **O**utcomes **P**rotection **E**valuation)[6] trial was designed to look at the effects of ramipril (Altase) on cardiovascular disease. This study was sponsored by the Medical Research Council of Canada, the Natural Source Vitamin E Association, Negma, Hoechst-Marion Roussel, AstraZeneca, King Pharmaceuticals, and the Heart and Stroke Foundation of Ontario. It included 9,257 participants who were either hypertensive or normotensive and were at high risk for cardiovascular outcomes. Participants were followed for 4.5 years. Ramipril, an angiotensin-converting enzyme (ACE) inhibitor, or a placebo was added to baseline therapy.

This study included 5,720 participants who did not have a known diagnosis of diabetes at randomization. In a post hoc analysis, 5.4% of the randomly assigned participants in the placebo arm were diagnosed with diabetes compared to only 3.6% of the participants who were randomized to ramipril. The results

from HOPE suggesting that ACE inhibitors may affect glucose metabolism and insulin physiology with resulting decrease in the occurrence of diabetes are being actively investigated.

The HOPE trial provided some of the background for the DREAM (**D**iabetes **RE**duction **A**ssessment With Ramipril and Rosiglitazone **M**edications) trial, which is sponsored by the Canadian Institute of Health. This is a multicenter, international, randomized, controlled trial of 4,000 subjects designed to determine if either ramipril or rosiglitazone (Avandia) will prevent or reduce the incidence of diabetes in individuals with IGT.

Because these two interventions have very different mechanisms of actions, the effects are likely to be independent and potentially complementary. Therefore, the trial has a two-by-two factorial design. Although the mechanism of action is unknown, ramipril may prevent diabetes through effects on β-cells and by vascular effects on muscle that may amplify the effects of insulin. Rosiglitazone appears to improve glucose sensitivity and may have a possible β-cell effect.

Participants will be assessed at regular intervals to determine the presence of diabetes as well as other secondary outcomes. Information about site locations can be found by calling 905-527-4322 ext. 44512.

Like DREAM, STOP NIDDM (**S**tudy **TO P**revent **N**on-**I**nsulin **D**ependent **D**iabetes **M**ellitus)[7] is designed to determine whether type 2 diabetes can be prevented. Sponsored by Bayer Corp., it is an international, multicenter trial of 1,418 participants with IGT and fasting plasma glucose >100 mg/dl. This ongoing study randomized participants to either acarbose (Precose; 100 mg three times a day) or placebo. Participants are expected to be followed for an average of 3.9 years. The primary outcome is the development of type 2 diabetes as diagnosed by a 75-g oral glucose tolerance test. Secondary outcomes will include changes in blood pressure, lipid profile, insulin sensitivity, and cardiovascular events.

Cardiovascular Disease

In addition to the exciting work that is being done to prevent diabetes, several ongoing studies are looking at ways to identify, prevent, and treat cardiovascular disease in patients with diabetes. Type 2 diabetes is now considered a cardiovascular risk equivalent,[8] and serious attempts are being made to identify those at highest risk and determine the best therapies for intervention. Among the ongoing studies in this area are BARI 2D, ACCORD, DIAD, and Look AHEAD. All of these studies are currently recruiting participants, and outcome data are not yet available

BARI 2D (**B**ypass **A**ngioplasty **R**evascularization **I**nvestigation in Type **2 D**iabetes) is a multicenter trial sponsored by the National Heart, Lung, and Blood Institute (NHLBI) and designed to determine the best treatment of established cardiovascular disease in people with type 2 diabetes. Patients are randomized to one of four groups: *1*) best medical therapy for cardiac disease and insulin-sensitizing drugs, *2*) best medical therapy for cardiac disease and insulin-providing drugs, *3*) surgical or balloon revascularization, best medical therapy for cardiac disease, and insulin-sensitizing drugs, or *4*) surgical or balloon revascularization, best medical therapy for cardiac disease, and insulin-providing drugs.

Investigators hope to recruit 2,600 patients over the next 2 years and to follow them for 5–7 years. The primary outcome is the 5-year all-cause mortality rate.

ACCORD (**A**ction to **C**ontrol **C**ardiovascular **R**isk in **D**iabetes) is a multicenter, randomized trial sponsored by the NHLBI and designed to determine whether major cardiovascular events in type 2 diabetes can be prevented by decreasing insulin resistance and intensively controlling glycemia, lipids, and blood pressure. This study has a three-by-two factorial design.

ACCORD is currently enrolling patients who are 50–75 years old and have type 2 diabetes controlled with diet or oral agents. Information about study sets can be obtained at www.clinicaltrials.gov.

DIAD (**D**etection of **I**schemia in **A**symptomatic **D**iabetics) is another multicenter, randomized, clinical trial and is designed to help determine ways to identify early ischemic disease in patients with type 2 diabetes. This study, sponsored by DuPont and Fujisawa, is currently recruiting 1,000 subjects aged 50 years or older who have type 2 diabetes through eight sites across the country. Subjects will be randomized to receive adenosine sestimibi SPECT imaging or regular follow-up. Investigators will look at the prevalence of myocardial perfusion imaging abnormalities in these asymptomatic patients and will be able to establish an association between perfusion abnormalities and adverse outcomes.

Look AHEAD (**A**ction for **HEA**lth in **D**iabetes) is a multicenter, randomized, clinical trial sponsored by several organizations including the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), NHLBI, the National Institute of Nursing Research (NINR), the Office of Research on Minority Health (ORMH), and the Office of Research on Women's Health (ORWH). It aims to examine the long-term effects on cardiovascular health of lifestyle intervention to achieve and maintain weight loss.

This trial is currently recruiting 5,000 people who have type 2 diabetes and are overweight to be randomized to one of two groups. One group will be counseled to eat fewer calories and increase exercise, whereas the second group will receive diabetes support and education. Information about study sites can be found at www.look AHEAD.org.

Genetics

Environmental factors contribute tremendously to the development of diabetes and its complications. However, genetic factors also play a role. Several ongoing studies are looking at the genetics of diabetes and its complications.

Among these are the GOCADAN and GoKinD studies.

GOCADAN (**G**enetics **O**f **C**oronary **A**rtery **D**isease in **A**laskan **N**atives) is sponsored by the NHLBI. Heart disease is the greatest health abnormality found in Alaskan Natives. This epidemiological study is looking at cardiovascular disease and risk factors in families living in Unalakleet or Koyuk, Alaska. Participants from 40 families will undergo a personal and family medical history, have a physical exam, undergo electrocardiogram and carotid ultrasound, and give blood specimens for DNA and cholesterol testing. With this information, investigators hope to be able to determine the genes that can cause or prevent heart disease in this population.

GoKinD (**G**enetics **o**f **Ki**d**n**ey in **D**iabetics) is a study sponsored by the National Center for Research Resources (NCRR) and the JDRF and designed to look at the role of genes in kidney disease for patients with type 1 diabetes. Because kidney disease runs in families, this study will evaluate DNA from more than 2,000 people with diabetes, with and without kidney disease. DNA samples from both probands and parents will be linked with clinical data. Genetic material and clinical data will be available to investigators to test hypotheses related to the genetics of diabetic nephropathy.

This study is still actively recruiting participants. Participants must be 18–54 years of age, have had type 1 diabetes for at least 10 years, and, if nephropathy is present, have no other causes of nephropathy. Study site information can be found on the JDRF Website www.jdfr.org or by calling 1866-4GO-KIND.

Therapies

In addition to the vast number of pharmaceutical trials being performed on a daily basis for new treatment for diabetes, the NIH, JDRF, ADA, and a variety of private sources sponsor many such trials. One study with a great acronym is the NEW DAY (**N**utrition, **E**xercise, **W**eight Loss, **Di**abetes **A**nd **Y**ou) trial. This is a small phase-three trial sponsored by the NIH and is underway at the University of Alabama. It is designed to determine whether adding individual motivational sessions to behavior group weight loss intervention will improve weight loss and glycemic control in women with type 2 diabetes. Clinicians anxiously await its conclusion.

With continued investigations, a new day may dawn in diabetes. As investigators strive for a cure, new acronyms will no doubt continue to flood the diabetes journals. Behind each acronym are teams of investigators and coordinators, thousands of hours of work, millions of dollars, and—most importantly—willing volunteers. Without those who look toward better ways for prevention and treatment for future generations, no trials would ever take place. Each study helps to answer a question and fosters new ideas for investigators as we Look AHEAD and HOPE and DREAM for a NEW DAY in which we STOP NIDDM and can say ENDIT to type 1 diabetes.

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