EPIDEMIOLOGY OF DIABETES INTERVENTIONS AND COMPLICATIONS (EDIC) STUDY

Description of Project

- The aim of EDIC is to study the clinical course and risk factors associated with the long-term complications of type 1 diabetes, using the cohort of the Diabetes Control and Complications Trial (DCCT).
- Overall study objectives of EDIC are:
    - To determine the effects and interactions of risk factors on the development and progression of atherosclerotic cardiovascular (coronary, peripheral and cerebral) disease;
    - To study the long-term evolution, and the effects and interactions of risk factors such as treatment, level of glycemia, hypertension, dyslipidemia, co-occurrence of other complications, and genetic factors, on the development and progression of microalbuminuria and diabetic nephropathy, advanced retinopathy, and clinically significant neuropathy;
    - To examine the long-term effects of conventional vs. intensive diabetes treatment during the DCCT on the subsequent development and progression of microvascular, neuropathic and cardiovascular complications;
    - To examine the effects of genetic factors, and interactions of these factors with other risk factors (e.g., glycemia, hypertension and treatment modalities), on the development and progression of these complications;
- Objectives of EDIC supported by special type 1 diabetes funding are:
    - To perform a repeat assessment of familial aggregation of diabetic complications with expanded data, and apply transmission disequilibrium testing to identify DNA sequence differences that influence susceptibility to diabetic complications;
    - To measure the onset and progression of subclinical cardiovascular disease by determination of carotid artery intimal medial thickness by ultrasound and coronary calcification by computed tomography using EBCT and multidetector scanning;
    - To determine the prevalence, incidence, and determinants of uropathic complications and other complications from autonomic neuropathy;

Accomplishments

- For the genetics studies:
    - Recruitment and clinical collection for family members of the DCCT/EDIC probands about 76% complete;
    - DNA is being transferred to the University of Toronto for ongoing assessment of DNA quality and sample authenticity;
    - Detailed analysis plan for individual based association analysis developed; plan for family-based association analysis developed;
    - Clinical dataset for genetic studies is being formatted;

    - Individual based association analysis of certain genotypes with retinopathy and microalbuminuria is ongoing;
    - Establishment of a genetics consortium among the University of Toronto and other collaborators who have DCCT/EDIC genetic samples.
- For the subclinical cardiovascular studies, progress includes:
    - Of the approximate 1,400 DCCT/EDIC participants, carotid ultrasonography completed in 1,325 in 1994-1995 and in 1,229 in 1998-2000;
    - Results from carotid ultrasounds of 1994-95 showed no difference between DCCT/EDIC subjects and age/sex matched controls and no difference between DCCT intensively treated and conventionally treated groups. Published in Diabetes, Vol 49, Feb 1999;
    - Results from carotid ultrasounds of 1998-2000 showed significantly greater carotid intima-medial wall thickness in EDIC cohort than in nondiabetic controls, and significantly less progression in DCCT intensively treated than conventionally treated group. Published in New England Journal of Medicine, June 5, 2003;
    - Coronary calcification studies were conducted in 1,205 EDIC subjects in 2000-2003;
    - Results from coronary calcification studies were presented at the American Diabetes Association in June 2003. Published in Diabetes Vol 52, Supplement 1, A152, June 2003 and Diabetologia, Supplement 2, A23-59, Aug. 2003. Manuscript is under review;
    - Carotid Ultrasound protocol scheduled to be repeated in 2004 - 2005;
    - Expert group assembled in April and September 2003, and advised consideration of cardiac MRI.
- For the urologic and autonomic neuropathy studies:
    - Separate self-administered questionnaires were developed for females and males to collect information on urinary incontinence, urinary tract infections, and sexual function;
    - A brochure containing information for EDIC subjects was developed, as well as informed consents and careful procedures to ensure confidentiality;
    - Data are being sent to Coordinating Center;
    - Analysis plans have been drafted;
    - As of April 2004, 1,067 EDIC patients completed the questionnaire;
    - Preliminary analyses are being reviewed by the Writing Team;
    - Expert group assembled in May 2002 and April and September 2003 and consultants have advised consideration of cardiac autonomic nerve function testing as well as repeat peripheral nerve testing;
- Recent, important and provocative findings are the persistent, long-term effects of intensive treatment and reduction in glycemia in the DCCT resulting in substantially reduced risk of retinopathy, nephropathy and neuropathy in EDIC, termed “metabolic memory.” (See NEJM 2000; 342:381-389, JAMA 2002;287:2563-2569, and JAMA 2003;290:2159-2167). This topic was the subject of a symposium in April 2003, honoring the 20th anniversary of the

DCCT/EDIC, which included participants from diverse disciplines to present and discuss the underlying mechanisms that may be responsible for this observation.

Future directions

- To perform a repeat assessment of familial aggregation of diabetic complications with expanded data, and apply transmission disequilibrium testing to identify DNA sequence differences that influence susceptibility to diabetic complications;
- To measure the onset and progression of subclinical cardiovascular disease by determination of carotid artery intimal medial thickness by ultrasound and other techniques;
- To determine the prevalence, incidence, and determinants of uropathic complications and other complications from autonomic neuropathy.

Materials to be made available to researchers

- DNA;
- Clinical and biochemical data;
- Serum, plasma, and urine specimens from the DCCT are currently being provided to the wider scientific community to conduct studies consistent with the aims of the DCCT/EDIC through advertisement in the NIH Guide and external and EDIC scientific review of applications (please visit http://www.niddk.nih.gov/patient/EDIC/edic.htm for more information);
- Data files from the DCCT are currently available to the wider scientific community through the National Technical Information Service.

Participants

Sponsor: National Institute of Diabetes and Digestive and Kidney Diseases

Study Chairmen
Saul Genuth, Case Western Reserve University
David Nathan, Harvard Medical School

Participating Institutions

Clinical Centers

Albert Einstein College of Medicine
Case Western Reserve University
Cornell University Medical Center
Henry Ford Health System
International Diabetes Center
Joslin Diabetes Center
Massachusetts General Hospital
Mayo Foundation
Medical University of South Carolina
Northwestern University
University of California, San Diego
University of Iowa
University of Maryland School of Medicine
University of Michigan
University of Minnesota

University of Missouri
University of New Mexico
University of Pennsylvania
University of Pittsburgh
University of South Florida
University of Tennessee
University of Texas Southwestern
University Medical Center
University of Toronto
University of Washington
University of Western Ontario
Vanderbilt University
Washington University, St. Louis
Yale University School of Medicine

Clinical Coordinating Center
Case Western Reserve University

Data Coordinating Center
The George Washington University, Biostatistics Center

Other
University of Wisconsin, Central Fundus Photograph Reading Center
University of Minnesota, Central Biochemistry Laboratory and Central ECG Reading Unit
New England Medical Center, Central Carotid Ultrasound Unit
Harbor UCLA Research and Education Institute, Computed Tomography Reading Center
Hospital for Sick Children, Genotyping and Genetic Analyses Center