POSITION STATEMENT

Prevention of Type I Diabetes Mellitus

BACKGROUND

Type I (insulin-dependent) diabetes mellitus is an autoimmune disease. Although the process by which the pancreatic β-cell is destroyed is not well understood, several risk factors and immune-related markers are known that accurately identify many first-degree relatives of patients with type I diabetes who will develop the disease. Because we now have the ability to predict the development of type I diabetes in some people, investigators have begun to explore the use of immune intervention therapy to halt or even prevent β-cell destruction in such individuals.

In view of the emerging interest in this area of investigation, in April 1990, the National Institutes of Health convened a workshop to discuss the many factors related to immunomodulation to prevent type I diabetes. The general consensus from the meeting was that indeed there is methodology that can identify, with near certainty among first-degree relatives of type I diabetic patients, those who will develop diabetes and that immune intervention therapy before the onset of symptoms might prevent the disease from occurring.

In June 1990, the American Diabetes Association (ADA) convened an ad hoc expert committee on the prevention of type I diabetes mellitus. The committee developed this position statement.

STATEMENT

General information

- Sufficient data exist to warrant intervention studies for the prevention of type I diabetes.
- Intervention for the prevention of type I diabetes should be attempted only in the context of defined clinical studies with Institutional Review Board oversight.
- Intervention studies for the prevention of type I diabetes are best accomplished by randomized controlled studies.
- A registry of intervention studies should be maintained, and all planned studies should be reported to a coordinating body.

Screening

- Screening of any population is discouraged outside the context of defined research studies.
- Screening of high-risk individuals (e.g., 1st-degree relatives of type I diabetic patients) should be encouraged, providing that individuals who screen positive are referred to centers participating in cooperative intervention studies or other scientific investigations. Information about ongoing studies should be easily obtainable.
- All patients screened and not entered into a study should be counseled as to their risk of diabetes, and follow-up should be offered.
- Currently, initial screening should be by measurement of cytoplasmic islet cell antibodies (ICAs) with an assay that is calibrated to the international standard and verified by participation in a proficiency testing program, e.g., the Immunology of Diabetes Workshop Proficiency Program (Gainesville, FL).
- Screening by determining HLA type is not currently warranted outside the context of defined research studies.

Study conduct

- All pharmacological intervention studies must meet applicable Food and Drug Administration and in-

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stitutional requirements regarding *1*) the use of investigational new drugs, *2*) investigator qualifications, *3*) Institutional Review Board review and approval, *4*) informed patient consent, and *5*) children who are research subjects. Studies conducted outside the United States should conform to equivalent requirements.
- All intervention studies should be peer reviewed and monitored by a qualified review committee not associated with the study.
- All intervention studies should use a consent process that ensures and documents full understanding of the protocol.
- Standardization of all methods, procedures, assays, entry criteria, and end-point definitions is essential to permit meaningful comparison between studies. When appropriate, the use of reference laboratories to accomplish this is recommended.
- All investigators should conform to the American College of Physicians postition statement of the interaction of physicians with the pharmaceutical industry.*

Study planning

- Definition of diabetes and impaired glucose tolerance
  -The definition of type I diabetes mellitus should be according to World Health Organization (WHO) criteria: fasting plasma glucose (FPG) ≥7.8 mM (≥140 mg/dl) on more than one occasion or hyperglycemia of >11.1 mM (>200 mg/dl) 2 h after ingesting a 1.75-g/kg (max 75-g) oral glucose load. Individuals fulfilling these criteria already have diabetes and should not be enrolled in a prevention study. Also, these criteria define a study outcome.
  -The definition of impaired glucose tolerance should also follow WHO criteria: FPG ≤7.8 mM (≤140 mg/dl) and plasma glucose 7.8–11.1 mM (140–200 mg/dl) 2 h after ingesting a 1.75-g/kg (max 75-g) oral glucose load. Individuals fulfilling these criteria should be identified and reported at the time of enrollment (if included in any given study) and as a study outcome.
  -Individuals who do not fulfill either definition at the time of study entry but who have had a previous abnormality of glucose tolerance should be identified and reported.
- Each study must be evaluated on the basis of its potential risks versus benefits. Children should not be excluded, on the basis of age alone, from a therapeutic study that may benefit them by preventing diabetes.
- To permit comparison between studies, all patients should be characterized by the following baseline tests: oral and intravenous† glucose tolerance tests (1st-phase insulin response), ICAs, and islet cell autoantibodies. These tests should be performed by standardized methodology, and critical samples (e.g., entry samples) should be sent to a reference laboratory for verification and/or use in eligibility. It is strongly recommended that cells and serum be saved for HLA typing and other tests that might become feasible in the future.
- All studies should specify their inclusion and exclusion criteria and management and study withdrawal criteria.
- Each study should have a single specified sample size and a specified primary end point. Sample-size calculations should include an analysis of statistical power for detecting treatment differences. The sample size should be sufficient to achieve a meaningful conclusion, or the study should not be undertaken. Statistical guidelines and an organizational structure for interim monitoring should be defined.

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†Standard protocol for intravenous glucose tolerance test: preparation by 3 days of unrestricted diet (at least 150 g CHO) and normal physical activity, then fasting for 10–16 h; test starting at 0730–1000. Procedure: 0.5 g/kg (max 35 g) of a 25% glucose solution infused over 3 min ± 15 s by manual- or pump-driven syringe and timed to ensure a steady infusion rate. Samples: 2 baseline samples 10 min apart and samples 1, 3, 5, and 10 min after the end of the glucose infusion. Sampling: single forearm vein cannula may be used but should be flushed with saline after the glucose is infused; dead space should be cleared before samples are drawn.