Validation of the Diabetes Prevention Trial-Type 1 Risk Score in the TrialNet Natural History Study

JAY M. SOSENKO, MD1
JAY S. SKYLER, MD2
JEFFREY MAHON, MD2
JEFFREY P. KRISCHER, PHD3
CRAIG A. BEAM, PHD3
DAVID C. BOULWARE, MS3
CARLA J. GREENBAUM, MD4
LISA E. RAFKIN, MS, CDE1
CATHERINE COWIE, PHD5
DAVID CUTHBERTSON, MS6
JERRY P. PALMER, MD7

CARLA J. GREENBAUM, MD4
DAVID C. BOULWARE, MS3
JEFFREY P. KRISCHER, PHD3
JEFFREY MAHON, MD2
JAY S. SKYLER, MD2
JAY M. SOSENKO, MD1

OBJECTIVE—We assessed the accuracy of the Diabetes Prevention Trial–Type 1 Risk Score (DPTRS), developed from the Diabetes Prevention Trial–Type 1 (DPT-1), in the TrialNet Natural History Study (TNNHS).

RESEARCH DESIGN AND METHODS—Prediction accuracy of the DPTRS was assessed with receiver-operating characteristic curve areas. The type 1 diabetes cumulative incidence within the DPTRS intervals was compared between the TNNHS and DPT-1 cohorts.

RESULTS—Receiver-operating characteristic curve areas for the DPTRS were substantial in the TNNHS (P < 0.001 at both 2 and 3 years). The type 1 diabetes cumulative incidence did not differ significantly between the TNNHS and DPT-1 cohorts within DPTRS intervals. In the TNNHS, 2-year and 3-year risks were low for DPTRS intervals <6.30 (<0.10 and <0.20, respectively). Thresholds ≥7.50 were indicative of high risk in both cohorts (2-year risks: 0.49 in the TNNHS and 0.51 in DPT-1).

CONCLUSIONS—The DPTRS is an accurate and robust predictor of type 1 diabetes in autoantibody-positive populations.

Diabetes Care 34:1785–1787, 2011

We developed a type 1 diabetes risk score (Diabetes Prevention Trial–Type 1 Risk Score [DPTRS]) from Diabetes Prevention Trial–Type 1 (DPT-1) data (1). However, because DPT-1 participants were islet cell antibody (ICA)-positive relatives of type 1 diabetic patients (2,3), it was not clear whether the DPTRS would accurately predict type 1 diabetes in other populations (4). Thus, we tested the performance of the DPTRS in the TrialNet Natural History Study (TNNHS) (5), in which entry was on the basis of different autoantibody criteria.

RESEARCH DESIGN AND METHODS—The TNNHS participants were described previously (5). They were relatives of type 1 diabetic patients, with at least one biochemical autoantibody (GAD65, ICA512, or mIAA) upon screening. Of 991 TNNHS subjects studied, 116 developed type 1 diabetes. Participants in the DPT-1 parental and oral insulin trials also have been described (2,3). They were ICA-positive relatives of individuals with type 1 diabetes. Of 670 DPT-1 subjects studied, 241 developed type 1 diabetes. Both DPT-1 and the TNNHS were approved by institutional review boards, and written informed consent was obtained in both studies.

In both studies, after the baseline 2-h oral glucose tolerance test (OGTT) was performed, participants were followed for the development of type 1 diabetes with 2-h OGTTs at 6-month intervals. For each OGTT, fasting samples were obtained before oral glucose administration and at 30, 60, 90, and 120 min. If an OGTT was in the diabetic range according to American Diabetes Association criteria, a confirmatory OGTT was performed unless it was deemed unnecessary from the clinical presentation (symptomatic or marked hyperglycemia). Diagnoses also were made between visits, according to clinical criteria.

Laboratory measures
Plasma glucose was measured by the glucose oxidase method. C-peptide was measured by radioimmunoassay in DPT-1. Fasting C-peptide values in the undetectable range (<0.2 ng/mL) were assigned a value of 0.1 ng/mL for the analyses. In the TNNHS, C-peptide was measured by an immunoenzymometric assay using the Tosoh 600 II autoanalyzer (Tosoh Bioscience, South San Francisco, CA) (6). In a previous analysis, 564 individuals had C-peptide measurements by both assays (r = 0.961; Tosoh = 0.96 × RAI + 0.1). A diabetic-range OGTT was defined as a fasting glucose value ≥126 mg/dL and/or a 2-h glucose value ≥200 mg/dL.

Data analysis
The DPTRS and its conversion to risk estimates have previously been described (1). Student t tests and $x^2$ tests were used to assess differences. Prediction accuracy was assessed with receiver-operating characteristic curves that were adjusted for censoring (7). Observed risks were plotted according to DPTRS intervals separately for the DPT-1.
and TNNHS cohorts. Proportional hazards regression was used to assess associations. Kaplan-Meier curves were calculated to describe the occurrence of type 1 diabetes. Log-rank testing was used to assess curve differences. SAS version 9.1.3 and SAS version 9.2 were used. All P values are two-sided; P values < 0.05 were considered statistically significant.

RESULTS—In comparisons of the DPTRS variables between TNNHS and DPT-1 participants, the former were older (18.5 ± 13.3 years vs. 13.9 ± 9.6 years), had higher BMI values (21.6 ± 6.11 kg/m² vs. 19.8 ± 5.0 kg/m²), and had a greater C-peptide sum (2.4 ± 0.9 ng/mL vs. 1.7 ± 0.7 ng/mL) and fasting C-peptide levels (1.5 ± 0.8 ng/mL vs. 1.0 ± 0.7 ng/mL) (P < 0.001 for all). DPTRS values of the TNNHS participants were significantly lower (P < 0.001), even though their glucose sum values were almost identical (5.2 ± 1.1 mg/dL vs. 5.3 ± 1.1 mg/dL) to those in DPT-1. All variables in the DPTRS model were predictive of type 1 diabetes in the TNNHS (P < 0.01), except for fasting C-peptide (P = 0.075).

We evaluated the prediction accuracy of the DPTRS in the TNNHS cohort with receiver-operating characteristic curves. The area under the curve for the DPTRS in the TNNHS participants was substantial at both 2 years (0.83; P < 0.001) and 3 years (0.80; P < 0.001).

Figure 1 shows observed 2-year and 3-year risks in the TNNHS and DPT-1 derived from cumulative incidence curves for DPTRS intervals. There were no significant differences between TNNHS and DPT-1 cumulative incidence curves for any interval. In the TNNHS, 2-year and 3-year risks were low for DPTRS intervals <6.50 (<0.10 and <0.20, respectively). Those with DPTRS values ≥7.50 were at high risk for type 1 diabetes (2-year risks: 0.49 in the TNNHS and 0.51 in DPT-1).

The application of the DPTRS is presented in the following hypothetical example. An 8-year-old with a BMI of 18.0 kg/m² (log = 2.89) has normal glucose tolerance with fasting, 30-, 60-, 90- and 120-min values of 80 mg/dL, 150 mg/dL, 160 mg/dL, 140 mg/dL, and 120 mg/dL, respectively. Fasting, 30-, 60-, 90-, and 120-min C-peptide values are 0.86 ng/mL (log = −0.151), 2.5 ng/mL, 3.1 ng/mL, 3.2 ng/mL, and 2.8 ng/mL, respectively. Using the DPTRS coefficients and the above information, the DPTRS value equals (1.569 × log BMI) + (−0.056 × age) + (0.813 × glucose sum from 30 to 120 min/100) + (−0.848 × C-peptide sum from 30 to 120 min/10) + (0.476 × log fasting C-peptide) = 7.66. This converts to a 3-year risk estimate of 0.59.

CONCLUSIONS—The DPTRS was highly accurate and robust in its prediction of type 1 diabetes in the TNNHS. Predictors of type 1 diabetes have been studied (8,9), but the DPTRS is the first risk score for type 1 diabetes that has been validated in a separate population.

The consistent associations of type 1 diabetes with BMI in the TNNHS and DPT-1 cohorts are of interest, given the hypothesis that adiposity and insulin resistance contribute to the development of not only type 2 diabetes but also type 1 diabetes (10,11). Because the glucose sum was almost identical in the two cohorts, other DPTRS variables conferred the higher risk in DPT-1.

The DPTRS separated those at high risk from those at low risk in the TNNHS. This was evident in the substantially different risks between those with DPTRS values <6.50 and DPTRS values ≥7.50. Thus, the DPTRS can accurately identify target populations in type 1 diabetes prevention trials.
The DPTRS seems to be consistent in predicting risk across autoantibody-positive populations. However, it is not known whether the use of the DPTRS can be extended to autoantibody-negative populations that still are at higher risk for type 1 diabetes, such as nonrelatives with a genetic predisposition.

The DPTRS has a potential clinical application. Autoantibodies and other markers could eventually be used in clinical settings to identify individuals at risk for type 1 diabetes, especially if treatments are developed to preserve β-cell function. The DPTRS could then be used to refine the prediction of risk in such individuals.

Acknowledgments—TrialNet is a clinical trials network funded by the National Institutes of Health through the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute of Allergy and Infectious Diseases, the Eunice Kennedy Shriver National Institute of Child Health and Human Development, the National Center for Research Resources, the Juvenile Diabetes Research Foundation International, and the American Diabetes Association.

No potential conflicts of interest relevant to this article were reported.

J.M.S. analyzed data and wrote the manuscript. J.S.S., J.M., and J.P.K. conducted the study and reviewed the manuscript. C.A.B. contributed to the statistical support and reviewed the manuscript. D.C.B. contributed to programming and statistical support and reviewed the manuscript. C.J.G., L.E.R., and C.C. conducted the study and reviewed the manuscript. J.P.P. conducted the study, reviewed the manuscript, and assisted in writing the manuscript.

References
1. Sosenko JM, Krischer JP, Palmer JP, et al.; Diabetes Prevention Trial-Type 1 Study Group. A risk score for type 1 diabetes derived from autoantibody-positive participants in the Diabetes Prevention Trial-Type 1. Diabetes Care 2008;31:528–533
2. Diabetes Prevention Trial-Type 1 Diabetes Study Group. Effects of insulin in relatives of patients with type 1 diabetes mellitus. N Engl J Med 2002;346:1685–1691
3. Diabetes Prevention Trial-Type 1 Diabetes Study Group. Effects of oral insulin in relatives of patients with type 1 diabetes. Diabetes Care 2005;28:1068–1076
4. Knip M. Should we screen for risk of type 1 diabetes? Diabetes Care 2008;31:622–623
5. Mahon JL, Sosenko JM, Rafkin-Mervis L, et al.; TrialNet Natural History Committee; Type 1 Diabetes TrialNet Study Group. The TrialNet Natural History Study of the Development of Type 1 Diabetes: objectives, design, and initial results. Pediatr Diabetes 2009;10:97–104
6. Goel A, Chiu H, Felton J, Palmer JP, Brooks-Worrell B. T-cell responses to islet antigens improves detection of autoimmune diabetes and identifies patients with more severe β-cell lesions in phenotypic type 2 diabetes. Diabetes 2007;56:2110–2115
7. Heagerty PJ, Lumley T, Pepe MS. Time-dependent ROC curves for censored survival data and a diagnostic marker. Biometrics 2000;56:337–344
8. Sosenko JM, Palmer JP, Greenbaum CJ, et al.; Diabetes Prevention Trial-Type 1 Study Group. Increasing the accuracy of oral glucose tolerance testing and extending its application to individuals with normal glucose tolerance for the prediction of type 1 diabetes. Diabetes Care 2007;30:38–42
9. Mrena S, Virtanen SM, Laippala P, et al.; Childhood Diabetes in Finland Study Group. Models for predicting type 1 diabetes in siblings of affected children. Diabetes Care 2006;29:662–667
10. Kibirige M, Metcalf B, Rentuka R, Wilkin TJ. Testing the accelerator hypothesis: the relationship between body mass and age at diagnosis of type 1 diabetes. Diabetes Care 2003;26:2865–2870
11. Betts P, Mulligan J, Ward P, Smith B, Wilkin T. Increasing body weight predicts the earlier onset of insulin-dependant diabetes in childhood: testing the ‘accelerator hypothesis’ (2). Diabet Med 2005;22:144–151