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

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RESEARCH DESIGN AND METHODS—Prediction accuracy of the DPTRS was assessed with receiver-operating characteristic curve areas. 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 <6.90 (<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.

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 ICA-positive relatives of individuals developed type 1 diabetes. Participants in the DPT-1 parenteral 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 tests (OGTTs) were 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 analyzer (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 χ2 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 = 2.96) has normal glucose tolerance with fasting, 30-, 60-, 90-, and 120-min values of 80 mg/dL, 160 mg/dL, 140 mg/dL, and 120 mg/dL, respectively. Fasting, 30-, 60-, 90-, and 120-min C-peptide values are 2.5 ng/mL (log = −0.149), 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

\[ \text{DPTRS} = (1.569 \times \log \text{BMI}) + (−0.056 \times \text{age}) + (0.813 \times \text{glucose sum from 30 to 120 min/100}) + (−0.848 \times \text{C-peptide sum from 30 to 120 min/10}) + (0.476 \times \log \text{fasting C-peptide}) = 7.78. \]

This converts to a 3-year risk estimate of 0.63.

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.

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