The Application of the Diabetes Prevention Trial–Type 1 Risk Score for Identifying a Preclinical State of Type 1 Diabetes

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OBJECTIVE—We assessed the utility of the Diabetes Prevention Trial–Type 1 Risk Score (DPTRS) for identifying individuals who are highly likely to progress to type 1 diabetes (T1D) within 2 years.

RESEARCH DESIGN AND METHODS—The DPTRS was previously developed from Diabetes Prevention Trial–Type 1 (DPT-1) data and was subsequently validated in the TrialNet Natural History Study (TNNHS). DPTRS components included C-peptide and glucose indexes from oral glucose tolerance testing, along with age and BMI. The cumulative incidence of T1D was determined after DPTRS thresholds were first exceeded and after the first occurrences of glucose abnormalities.

RESULTS—The 2-year risks after the 9.00 DPTRS threshold was exceeded were 0.88 and 0.77 in DPT-1 ($n = 90$) and the TNNHS ($n = 69$), respectively. In DPT-1, the 2-year risks were much lower after dysglycemia first occurred (0.37; $n = 306$) and after a 2-h glucose value between 190 and 199 mg/dL was first reached (0.64; $n = 59$). Among those who developed T1D in DPT-1, the 9.00 threshold was exceeded 0.81 ± 0.53 years prior to the conventional diagnosis. Post-challenge C-peptide levels were substantially higher ($P = 0.001$ for 30 min; $P < 0.001$ for other time points) when the 9.00 threshold was first exceeded compared with the levels at diagnosis.

CONCLUSIONS—A DPTRS threshold of 9.00 identifies individuals who are very highly likely to progress to the conventional diagnosis of T1D within 2 years and, thus, are essentially in a preclinical diabetic state. The 9.00 threshold is exceeded well before diagnosis, when stimulated C-peptide levels are substantially higher.

Diabetes Care 35:1552–1555, 2012

Current diagnostic glucose thresholds for clinical type 1 diabetes (T1D) are based on the levels at which diabetes complications begin to occur; moreover, they are the same for type 2 diabetes (1). Yet it is known that the pathogenetic development of T1D begins well before those thresholds are reached. Pancreatic autoantibodies are commonly present a number of years before diagnosis (2–4). In addition, glucose, insulin, and C-peptide abnormalities are commonly present years before diagnosis (5–8). However, as yet, there has not been a means to identify individuals who will almost certainly be diagnosed within a few years.

A risk score (DPTRS) for T1D has been developed from Diabetes Prevention Trial–Type 1 (DPT-1) participants, all islet cell autoantibody positive, which utilizes oral glucose tolerance test (OGTT) glucose and C-peptide values, age, and BMI (9). The DPTRS was subsequently validated in the TrialNet Natural History Study (TNNHS), a separate cohort of biochemical autoantibody-positive individuals (10).

The strong prediction accuracy of the DPTRS suggested the possibility that it could be used to detect a preclinical state prior to the diagnosis of T1D. Thus, in both the DPT-1 and TNNHS cohorts, we have sought to detect a DPTRS threshold that might identify individuals at a sufficiently high 2-year risk for T1D to warrant the characterization of their being in a preclinical state. In addition, we have assessed the metabolic status of those individuals when such a threshold was exceeded.

RESEARCH DESIGN AND METHODS

The DPT-1 and TNNHS cohorts have been previously described (5,6). They both consisted of autoantibody-positive relatives of T1D patients. However, whereas the DPT-1 participants were all islet cell autoantibody positive, the TNNHS participants were all positive for at least one biochemical autoantibody (GADA, IA-2A, mIAA). Both DPT-1 and the TNNHS were approved by institutional review boards, and written informed consent was obtained for both studies.

Procedures

In both DPT-1 and the TNNHS, 2-h OGTTs were performed at 6-month intervals. Oral glucose was administered after fasting samples were obtained (1.75 g/kg; maximum, 75 g carbohydrate). Glucose samples were then obtained at 30, 60, 90, and 120 min. A diabetic range OGTT (by American Diabetes Association criteria) was followed by a confirmatory OGTT

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Received 3 January 2012 and accepted 18 March 2012.
DOI: 10.2337/dc12-0011

unless the clinical presentation (symptomatic or marked hyperglycemia) was indicative of the diagnosis. If an OGTT was not confirmed, participants were then followed in the routine manner. Diagnoses could also be made between visits according to clinical criteria.

Laboratory measures

The glucose oxidase method was used for plasma glucose measurements. A radioimmunoassay was used to measure C-peptide in DPT-1. If fasting C-peptide values were in the undetectable range (<0.2 ng/mL), they were assigned a value of 0.1 ng/mL. The methodologies for assessing autoantibody positivity in DPT-1 have been described (11); those same methodologies were used in the TNNHS.

Data analysis

The development of the DPTRS from DPT-1 data (9) and its validation in the TNNHS (10) has been described previously. In brief, the DPTRS is based on a proportional hazards model. The components of the DPTRS are age, log BMI, log fasting C-peptide, and the glucose and C-peptide sums of 30-, 60-, 90-, and 120-min values from OGTTs. Dysglycemia was defined by any of the following: fasting glucose 110–125 mg/dL; 30-, 60-, or 90-min glucose ≥200 mg/dL; 120-min glucose 140–199 mg/dL. Follow-up was calculated from when DPTRS thresholds were first exceeded. Some of the analyses were performed only with DPT-1 data since the numbers of those who exceeded thresholds during follow-up were larger. If a BMI measurement was not obtained at a visit, the measurement obtained at the prior visit (if within 9 months) was used. Paired *t* tests were used to examine differences. Proportional hazards regression was used for risk prediction. Kaplan-Meier curves were calculated to describe the occurrence of T1D. Analyses were performed with the SAS 9.1.3 and SAS 9.2 versions. *P* values are two-sided, and $P < 0.05$ was considered statistically significant.

RESULTS—The mean ± SD ages of the 674 DPT-1 and 1,202 TNNHS participants from whom the analyses were derived were 13.8 ± 9.5 and 18.3 ± 13.4 years, respectively.

There were 7 (1.0%) participants in DPT-1 and 14 (1.2%) in the TNNHS who had already exceeded the 9.00 DPTRS threshold at baseline and were therefore excluded from further analysis. Figure 1 shows cumulative incidence curves after the 9.00 threshold was first exceeded in DPT-1 (T1D/Total = 78/90) and the TNNHS (T1D/Total = 40/69). The curves were similar with 2-year risk estimates of 0.88 (95% CI 0.79–0.94) for DPT-1 and 0.77 (0.63–0.99) for the TNNHS. Only 3 of those not diagnosed in DPT-1 and 1 of those not diagnosed in the TNNHS were followed for >3.0 years. The 2-year estimates after the 8.75 DPTRS threshold was first exceeded were 0.82 (0.74–0.89) in DPT-1 ($n = 115$) and 0.70 (0.56–0.83) in the TNNHS ($n = 75$). When a threshold of 8.00 was exceeded, the 2-year estimates were lower but still >0.50 in both cohorts (0.73 [0.65–0.80] in DPT-1 and 0.54 [0.43–0.66] in the TNNHS). The numbers exceeding that threshold were appreciably greater ($n = 173$ in DPT-1 and $n = 114$ in the TNNHS) than the numbers exceeding the higher thresholds.

Figure 2 shows cumulative incidence curves of DPT-1 participants after dysglycemia first occurred ($n = 306$) and after a 2-h glucose value between 190 and 199 mg/dL was first reached ($n = 59$). (That interval was chosen to identify individuals with marked postchallenge hyperglycemia.) The curve after exceeding the 9.00 threshold is again shown for comparison. The cumulative incidence was much higher after exceeding the 9.00 DPTRS threshold (2-year risk 0.88 [95% CI 0.79–0.94]; $n = 90$) than the cumulative incidence after dysglycemia first occurred (2-year risk 0.37 [0.31–0.44]; $n = 306$). The cumulative incidence was also substantially higher after exceeding the 9.00 threshold than after a 190–199 mg/dL 2-h value was reached (2-year risk 0.64 [0.53–0.80]; $n = 59$). The 2-year risk for the 9.00 threshold was still appreciably higher (0.80 [0.67–0.89]; $n = 59$) even with the exclusion of those who had exceeded that threshold with diabetic range OGTTs that were not confirmed by a second OGTT.

Among the 44 participants with complete OGTTs at diagnosis, the 9.00 DPTRS threshold was first exceeded 0.81 ± 0.53 years earlier than at diagnosis ($P < 0.001$). Figure 3 shows C-peptide levels according to the time the 9.00 threshold was first exceeded and at diagnosis for those individuals. All postchallenge C-peptide levels were substantially higher ($P = 0.001$ for 30 min; $P < 0.001$ for other time points) when the 9.00 DPTRS threshold was first exceeded compared with the levels at diagnosis. Fasting C-peptide values were similar.

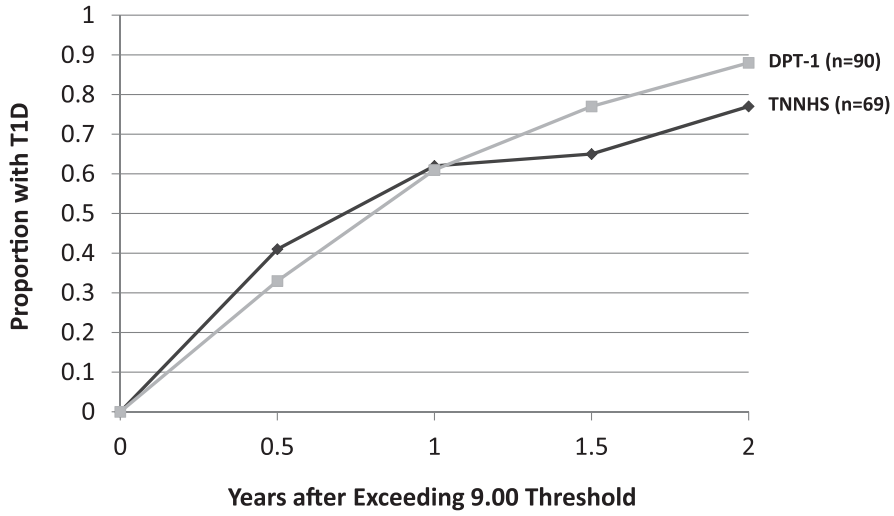

Figure 1—*Cumulative incidence curves after the 9.00 DPTRS threshold was first exceeded in DPT-1 and the TNNHS. The occurrence of T1D was substantial in both cohorts, and the curves were similar.*

CONCLUSIONS—The data in this report strongly suggest that a selected DPTRS threshold can be used as a marker that is firmly indicative of a preclinical state. In both the DPT-1 and TNNHS cohorts, those who exceeded the 9.00 threshold had a very high likelihood of progressing to T1D within 2 years. They were identified on average >9 months before the standard diagnosis, when stimulated C-peptide levels were considerably higher.

To gain perspective, the risk of T1D after the 9.00 DPTRS threshold was exceeded was compared with the risk of T1D after dysglycemia first occurred. Dysglycemia has

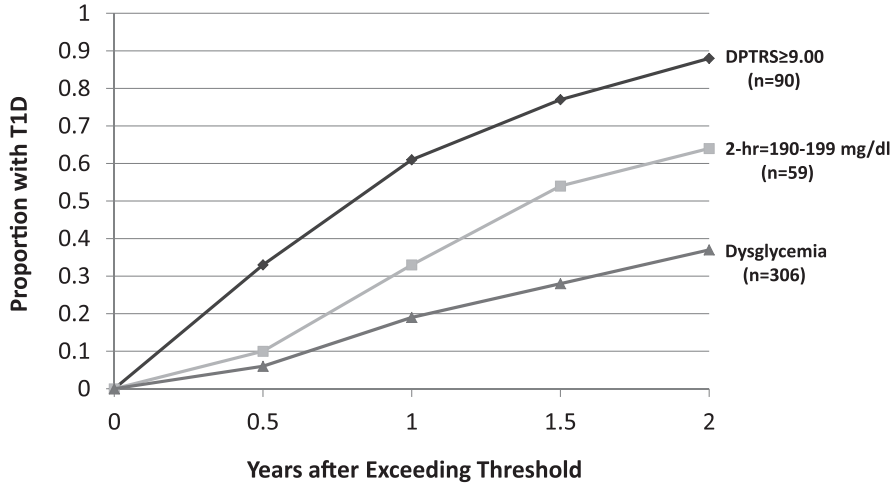

Figure 2—*Cumulative incidence curves after the 9.00 DPTRS threshold was first exceeded, after dysglycemia first occurred, and after the 2-h glucose value between 190 and 199 mg/dL was first reached in the DPT-1 participants. The cumulative incidence for the 9.00 threshold was much greater than that for dysglycemia and even appreciably higher than that for the 190–199 mg/dL 2-h glucose.*

been used to identify individuals at high risk for T1D (5). The substantially higher risk after exceeding the 9.00 threshold emphasizes the magnitude of the risk for individuals above that threshold.

OGTT surveillance was a key factor for identifying those at very high risk for T1D. Many more were found to be above the 9.00 threshold during follow-up than at baseline. (The number that exceeded the 9.00 threshold is almost certainly an underestimation since missing BMI values on certain visits precluded the calculation of the DPTRS.) Thus, through OGTT surveillance, DPTRS thresholds identify individuals who are at very high risk before they develop clinical signs and symptoms. Since it would not be feasible to perform OGTT surveillance on large numbers of individuals, the use of DPTRS thresholds for the detection of a preclinical T1D state is applicable to only higher-risk populations that might warrant such surveillance (e.g., those positive for autoantibodies).

DPTRS thresholds have potential utility as entry criteria for prevention trials of very high-risk individuals. C-peptide levels would be much higher in those individuals than in those entered into new-onset trials (12–14). Importantly, the identification of individuals at very high short-term risk would affect the risk-benefit considerations for children in prevention trials.

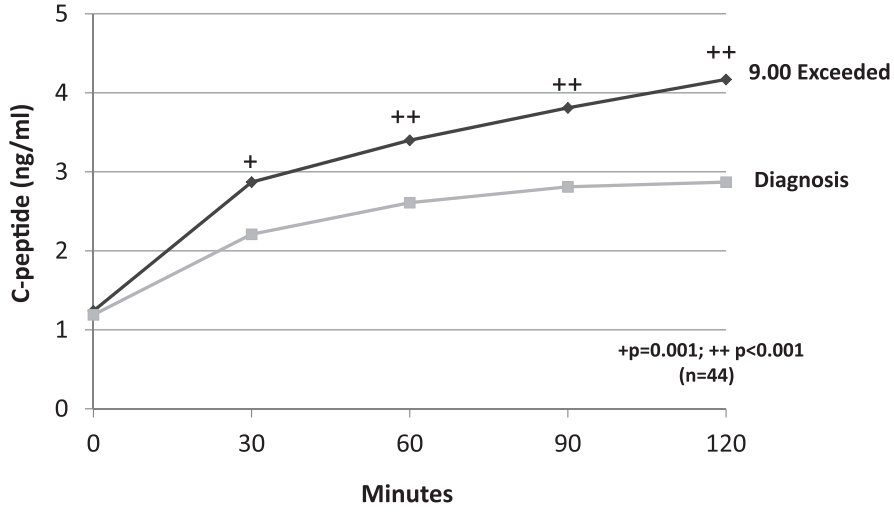

Figure 3—*Paired comparisons between C-peptide levels when the 9.00 DPTRS threshold was first exceeded and C-peptide levels at diagnosis in the DPT-1 participants. C-peptide levels were higher at all postchallenge time points.*

Alternatively, a high DPTRS threshold could be used in T1D prevention trials for interim analyses or as an end point that is adjunctive to the current diagnostic criteria. Our use of the term *preclinical type 1 diabetes* stems from the very high risk of a subsequent diagnosis of T1D for those exceeding the 9.00 threshold. Although T1D might not necessarily be an inevitable outcome in these individuals, the risk is so high that it is reasonable to view them as being in a prediabetic state.

T1D predictors have been reported in several studies (9,10,15–18). However, although individuals could be characterized as being at high risk, studies have not identified such individuals within a time frame of 2 years. The specific DPTRS threshold that might be used for the detection of preclinical T1D depends on the desired degree of certainty of an ultimate diagnosis. More individuals would be identified by a lower threshold, but the 9.00 threshold provides more assurance that T1D will occur over a short interval. This was evident in the data presented for the 8.75 and the 8.00 thresholds. Although we have conservatively chosen the 9.00 threshold to define a preclinical T1D state, it is arguable that lower thresholds could be used. In both DPT-1 and the TNNHS, even the 8.00 threshold identified individuals at substantially higher risk than those who developed dysglycemia in DPT-1. The ultimate choice of a threshold would be dependent upon the particular research needs and objectives.

The higher postchallenge C-peptide values at the time the 9.00 threshold was exceeded are consistent with our prior DPT-1 findings (7,8) in which values fell markedly from 6 months before diagnosis to diagnosis. This could very possibly be indicative of a loss of β-cell function. Since the 9.00 threshold was exceeded an average of >9 months before diagnosis, the lower C-peptide values at diagnosis would be expected.

The glucose criteria for T1D used in this report have been the "gold standard" for years. Those criteria were based on the rationale of defining a threshold according to the occurrence of complications (1). The possibility of preserving β-cell function provides an alternative rationale for identifying T1D at an earlier stage of its development. The persistence of C-peptide in Diabetes Control and Complications Trial participants was associated with a decreased risk of complications (19,20). The substantially higher C-peptide levels at the time the 9.00 threshold was first exceeded suggest that it would be more advantageous

to intervene in that preclinical diabetic state than at diagnosis. Although no treatment is known to preserve insulin secretion before diagnosis, the efficacy of treatments in new-onset patients (12–14) indicates that this is a distinct possibility.

In conclusion, this study shows that it is now possible to identify individuals who are in a state of preclinical T1D, when C-peptide levels are appreciably higher. It appears that a 9.00 DPTRS threshold can be used for this purpose in autoantibody-positive populations.

Acknowledgments—This work was 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 for Child Health and Human Development, and the National Center for Research Resources; by the Juvenile Diabetes Research Foundation International; and by 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., J.P.K., C.J.G., L.E.R., and C.C. conducted the study and reviewed the manuscript. C.A.B. provided statistical support. D.C.B. and D.C. provided programming and statistical support. J.P.P. conducted the study and wrote and reviewed the manuscript. J.M.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Parts of this study were presented in abstract form at the 71st Scientific Sessions of the American Diabetes Association, San Diego, California, 24–28 June 2011.

References

1. Diagnosis and classification of diabetes mellitus. Diabetes Care 2011;34(Suppl. 1):62–69
2. Gorsuch AN, Spencer KM, Lister J, et al. Evidence for a long prediabetic period in type I (insulin-dependent) diabetes mellitus. Lancet 1981;2:1363–1365
3. Palmer JP, Asplin CM, Clemons P, et al. Insulin antibodies in insulin-dependent diabetics before insulin treatment. Science 1983;222:1337–1339
4. Baekkeskov S, Landin M, Kristensen JK, et al. Antibodies to a 64,000 Mr human islet cell antigen precede the clinical onset of insulin-dependent diabetes. J Clin Invest 1987;79:926–934
5. 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
6. Skyler JS, Krischer JP, Wolfsdorf J, et al. Effects of oral insulin in relatives of patients with type 1 diabetes: The Diabetes Prevention Trial-Type 1. Diabetes Care 2005;28:1068–1076
7. Sosenko JM, Palmer JP, Greenbaum CJ, et al. Patterns of metabolic progression to type 1 diabetes in the Diabetes Prevention Trial-Type 1. Diabetes Care 2006;29:643–649
8. Sosenko JM, Palmer JP, Rafkin LE, et al.; Diabetes Prevention Trial-Type 1 Study Group. Trends of earlier and later responses of C-peptide to oral glucose challenges with progression to type 1 diabetes in Diabetes Prevention Trial-Type 1 participants. Diabetes Care 2010;33:620–625
9. 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
10. Sosenko JM, Skyler JS, Mahon J, et al.; Type 1 Diabetes TrialNet and Diabetes Prevention Trial-Type 1 Study Groups. Validation of the Diabetes Prevention Trial-Type 1 Risk Score in the TrialNet Natural History Study. Diabetes Care 2011;34:1785–1787
11. Orban T, Sosenko JM, Cuthbertson D, et al.; Diabetes Prevention Trial-Type 1 Study Group. Pancreatic islet autoantibodies as predictors of type 1 diabetes in the Diabetes Prevention Trial-Type 1. Diabetes Care 2009;32:2269–2274
12. Herold KC, Hagopian W, Auger JA, et al. Anti-CD3 monoclonal antibody in new-onset type 1 diabetes mellitus. N Engl J Med 2002;346:1692–1698
13. Pescovitz MD, Greenbaum CJ, Krause-Steinrauf H, et al.; Type 1 Diabetes TrialNet Anti-CD20 Study Group. Rituximab, B-lymphocyte depletion, and preservation of beta-cell function. N Engl J Med 2009; 361:2143–2152
14. Orban T, Bundy B, Becker DJ, et al.; Type 1 Diabetes TrialNet Abatacept Study Group. Co-stimulation modulation with abatacept in patients with recent-onset type 1 diabetes: a randomized, double-blind, placebo-controlled trial. Lancet 2011; 378:412–419
15. Mrena S, Virtanen SM, Laippala P, et al. Models for predicting type 1 diabetes in siblings of affected children. Diabetes Care 2006;29:662–667
16. 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: The Diabetes Prevention Trial-Type 1. Diabetes Care 2007; 30:38–42
17. Barker JM, McFann K, Harrison LC, et al.; DPT-1 Study Group. Pre-type 1 diabetes dysmetabolism: maximal sensitivity achieved with both oral and intravenous glucose tolerance testing. J Pediatr 2007; 150:31–36, e6
18. Xu P, Wu Y, Zhu Y, et al.; Diabetes Prevention Trial-Type 1 (DPT-1) Study Group. Prognostic performance of metabolic indexes in predicting onset of type 1 diabetes. Diabetes Care 2010;33:2508–2513
19. Steffes MW, Sibley S, Jackson M, Thomas W. Beta-cell function and the development of diabetes-related complications in the diabetes control and complications trial. Diabetes Care 2003;26:832–836
20. The Diabetes Control and Complications Trial Research Group. Effect of in-tensive therapy on residual beta-cell function in patients with type 1 diabetes in the diabetes control and complications trial. A randomized, controlled trial. Ann Intern Med 1998;128:517–523