



Use of the Diabetes Prevention Trial-Type 1 Risk Score (DPTRS) for Improving the Accuracy of the Risk Classification of Type 1 Diabetes

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OBJECTIVE

We studied the utility of the Diabetes Prevention Trial-Type 1 Risk Score (DPTRS) for improving the accuracy of type 1 diabetes (T1D) risk classification in TrialNet Natural History Study (TNNHS) participants.

RESEARCH DESIGN AND METHODS

The cumulative incidence of T1D was compared between normoglycemic individuals with DPTRS values >7.00 and dysglycemic individuals in the TNNHS ($n = 991$). It was also compared between individuals with DPTRS values <7.00 or >7.00 among those with dysglycemia and those with multiple autoantibodies in the TNNHS. DPTRS values >7.00 were compared with dysglycemia for characterizing risk in Diabetes Prevention Trial-Type 1 (DPT-1) ($n = 670$) and TNNHS participants. The reliability of DPTRS values >7.00 was compared with dysglycemia in the TNNHS.

RESULTS

The cumulative incidence of T1D for normoglycemic TNNHS participants with DPTRS values >7.00 was comparable to those with dysglycemia. Among those with dysglycemia, the cumulative incidence was much higher ($P < 0.001$) for those with DPTRS values >7.00 than for those with values <7.00 (3-year risks: 0.16 for <7.00 and 0.46 for >7.00). Dysglycemic individuals in DPT-1 were at much higher risk for T1D than those with dysglycemia in the TNNHS ($P < 0.001$); there was no significant difference in risk between the studies among those with DPTRS values >7.00 . The proportion in the TNNHS reverting from dysglycemia to normoglycemia at the next visit was higher than the proportion reverting from DPTRS values >7.00 to values <7.00 (36 vs. 23%).

CONCLUSIONS

DPTRS thresholds can improve T1D risk classification accuracy by identifying high-risk normoglycemic and low-risk dysglycemic individuals. The 7.00 DPTRS threshold characterizes risk more consistently between populations and has greater reliability than dysglycemia.

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Since the selection of participants for type 1 diabetes (T1D) prevention trials is based in large part on risk estimation, it is important to classify risk as accurately as possible. Study populations in those trials consist mainly of children, and the experimental treatments usually entail some degree of risk. Thus, a more accurate classification of risk would reduce potential harm in a vulnerable population. Improved risk classification could also result in a better assessment of efficacy with more representativeness of the findings by the inclusion of appropriate trial participants. Moreover, it could increase study efficiency by identifying more potential participants at high risk for T1D.

Prevention trials have used the presence of autoantibodies and dysglycemia (abnormal glucose levels, but not in the diabetic range) to define the risk for T1D on the basis of available data (1–4). However, newer findings suggest that a reliance on dysglycemia to define risk could fail to optimize risk classification. Those with normoglycemia could be at substantial risk, since glucose levels within the normal range are predictive of T1D in autoantibody-positive individuals (5,6). Moreover, certain individuals with dysglycemia might not be at high risk, since other factors (7) could attenuate that risk.

We have developed a T1D risk score (Diabetes Prevention Trial-Type 1 Risk Score [DPTRS]) from Diabetes Prevention Trial-Type 1 (DPT-1) data (7) that uses other factors, including the full range of glycemia, age, BMI, and C-peptide levels. The DPTRS was subsequently validated in the TrialNet Natural History Study (TNNHS) (8). This report will examine the use of the DPTRS for improving the accuracy of the risk classification of T1D.

RESEARCH DESIGN AND METHODS

Subjects

Participants were autoantibody-positive relatives of T1D patients from the DPT-1 ($n = 670$) and TNNHS ($n = 991$) cohorts. These cohorts have been previously described (9–11). DPT-1 participants were all islet cell autoantibody (ICA) positive, whereas TNNHS participants were all positive for GADA, IA-2A, mIAA,

and/or ICA. Both studies were approved by institutional review boards at all participating sites, and written informed consent or assent as appropriate were obtained in both studies.

Procedures

Two-hour oral glucose tolerance tests (OGTTs) were performed at baseline and at 6-month intervals in both cohorts. Oral glucose (1.75 g/kg; maximum, 75 g of carbohydrate) was administered after fasting samples were obtained; glucose and C-peptide samples were then obtained every 30 min. The diagnosis of T1D was based on American Diabetes Association criteria.

Laboratory Measures

Plasma glucose was measured by the glucose oxidase method. In DPT-1, C-peptide was measured by radioimmunoassay, whereas in the TNNHS, the TOSOH assay was used. Values from the two assays were similar in split samples ($r = 0.961$; TOSOH = $0.96 * \text{RAI} + 0.1$; $n = 564$). Undetectable fasting C-peptide values (<0.2 ng/mL) were assigned a value of 0.1 ng/mL. The methodology for performing autoantibody measurements in the TNNHS has been reported previously (12). The autoantibodies obtained in the TNNHS include ICA, GADA, mIAA, IA-2A, and ZnT8A. However, measurements of the latter were not obtained when the TNNHS was initiated. Thus, of the 991 studied, there are ZnT8A measurements in 548. Venous blood was used for measurements.

Data Analysis

The DPTRS (7), developed from the DPT-1 cohort, is based on a proportional hazards model that includes the glucose sum of 30-, 60-, 90-, and 120-min values divided by 100, the C-peptide sum of 30-, 60-, 90-, and 120-min values divided by 10, log fasting C-peptide, log BMI, and age. Each contributed significantly to the prediction of T1D. There is a curvilinear relation between risk and the DPTRS. As DPTRS values increase above 6.50, the risk estimates increase more steeply (8). The DPTRS was subsequently validated in the TNNHS (8). Dysglycemia was defined as any of the following on the baseline OGTT: a fasting glucose value between 110 and 125 mg/dL (impaired fasting glucose); a

30-, 60-, and/or 90-min value ≥ 200 mg/dL with a 2-h value <140 mg/dL (indeterminate); or a 2-h value between 140 and 199 mg/dL (impaired glucose tolerance [IGT]). Participants were informed if they had a dysglycemic OGTT; however, no treatment was recommended. Analyses included the following: a comparison of the cumulative incidence of T1D between normoglycemic individuals with DPTRS values >7.00 and those with dysglycemia; a comparison of the cumulative incidence of T1D between DPTRS values <7.00 or >7.00 among those with dysglycemia and among those with two or more autoantibodies; a comparison of the cumulative incidence of T1D between the TNNHS and DPT-1 among those with DPTRS values >7.00 and among those with dysglycemia; and a comparison of the reliability between DPTRS values >7.00 and dysglycemia. The 7.00 threshold had previously been shown to identify high-risk individuals in the overall DPT-1 and TNNHS cohorts (8). χ^2 tests and Student t tests were used for comparisons between groups. T1D occurrence was described by cumulative incidence curves. The log-rank test was used to examine differences between cumulative incidence curves. The SAS 9.1.3 and SAS 9.2 versions were used for the analyses. The P values are two-sided. A P value <0.05 was considered to be statistically significant.

RESULTS

The 991 TNNHS participants were significantly older than the 670 DPT-1 participants (mean age \pm SD: 18.5 ± 13.3 years [median 13.0 years] vs. 13.8 ± 9.6 years [median 11.1 years]; $P < 0.001$). In the TNNHS, 45% were male, whereas in DPT-1, 56% were male. Of the 991 studied in the TNNHS, 116 (12%) were diagnosed. The median follow-up of those diagnosed and those not diagnosed was 1.4 and 2.0 years, respectively. There were 221 (22%) who had dysglycemia at baseline. The majority of those with dysglycemia had IGT. Whereas 125 had IGT alone, 29 had an indeterminate OGTT alone, and 7 had impaired fasting glucose alone.

Figure 1 shows that a DPTRS threshold >7.00 identified TNNHS participants with normoglycemia at baseline who

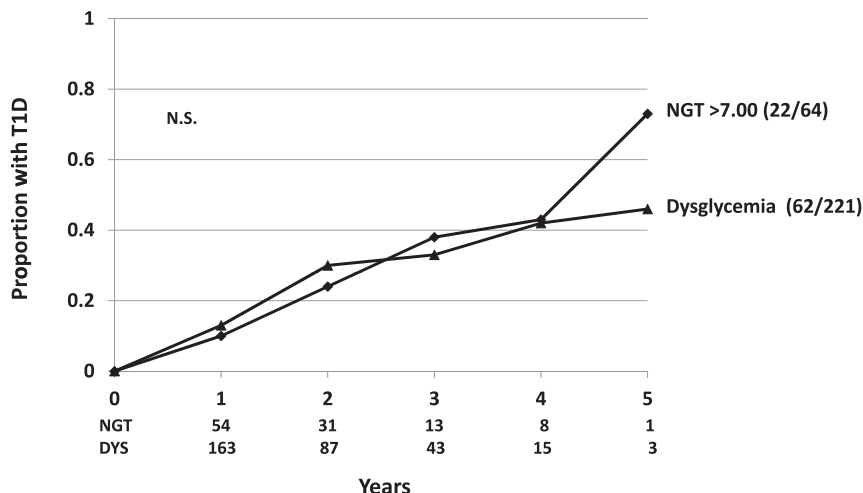


Figure 1—Shown are cumulative incidence curves for T1D of TNNHS participants with normoglycemia (NGT) and DPTRS values >7.00, or with dysglycemia. The cumulative incidence curves are comparable. N.S., not significant.

were at substantial risk for T1D. The cumulative incidence of TNNHS participants with normoglycemia and DPTRS values >7.00 was comparable to the cumulative incidence of those with dysglycemia. The 3-year risk estimates were 0.38 for those with DPTRS values >7.00 and 0.33 for those with dysglycemia. TNNHS participants with normoglycemia and DPTRS values >7.00 were much younger than those with dysglycemia (8.1 ± 4.9 years for DPTRS >7.00 vs. 19.6 ± 14.3 years for dysglycemia; $P < 0.001$).

When those in the TNNHS with dysglycemia were dichotomized according to DPTRS values >7.00 or <7.00 (Fig. 2), there was a marked difference between the cumulative incidence curves ($P < 0.001$). TNNHS participants with dysglycemia and DPTRS values <7.00 were at relatively low risk for T1D. The 3-year risk estimate was 0.46 for those >7.00, whereas the 3-year risk estimate was only 0.16 for those <7.00. The 3-year risk for those with normoglycemia and DPTRS values <7.00 was 0.08.

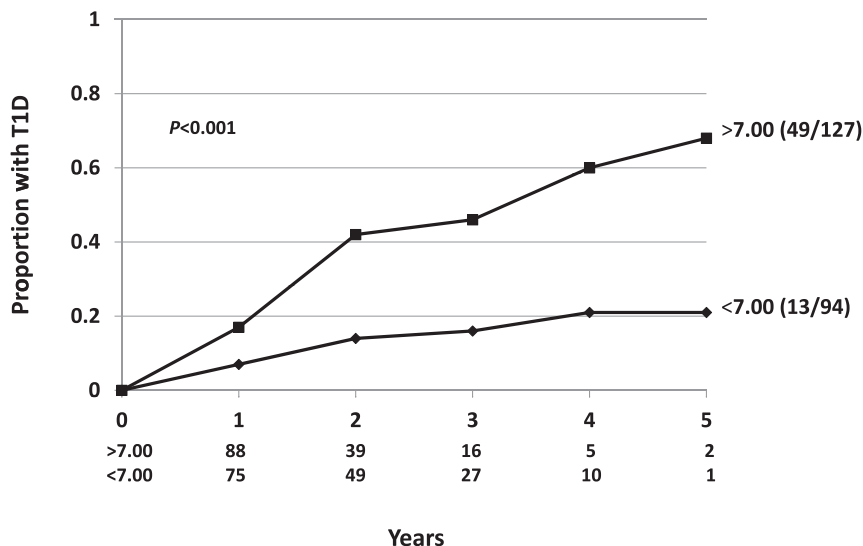


Figure 2—Shown are cumulative incidence curves of TNNHS participants with dysglycemia after they are dichotomized according to DPTRS values <7.00 or >7.00. There is a large difference in the cumulative incidence (3-year estimates: 0.16 for <7.00 and 0.46 for >7.00).

We also assessed the differences in risk according to the 7.00 DPTRS threshold among individuals with two or more autoantibodies in the TNNHS. There was again a marked difference in risk ($P < 0.001$ for difference in cumulative incidence curves). Individuals with DPTRS values >7.00 ($n = 87$) had a 3-year risk estimate of 0.55, whereas those with DPTRS values <7.00 ($n = 209$) had a 3-year risk estimate of 0.16.

The degree of consistency in estimating risk between DPT-1 and the TNNHS is shown for those with DPTRS values >7.00 in Fig. 3A and those with dysglycemia in Fig. 3B. Whereas there was no significant difference in the cumulative incidence of T1D between DPT-1 and TNNHS participants for those with DPTRS values >7.00, the cumulative incidence for those with dysglycemia was much higher in DPT-1 than in the TNNHS ($P < 0.001$).

Reliability was also compared between dysglycemia and the 7.00 DPTRS threshold. Of those who had dysglycemia at baseline in the TNNHS, 77 of 213 (36%) reverted to normoglycemia at the next visit. Of the 77, 41 (53%) had DPTRS values <7.00 at baseline. Of those with DPTRS values >7.00 at baseline, a smaller proportion, 42 of 177 (24%), reverted to having values <7.00 at the next visit. Of the 42, 22 (52%) had normoglycemia at baseline. Of those with DPTRS values >7.00 who reverted to DPTRS values <7.00, the glucose sum declined significantly ($P < 0.001$). There was a decline in the C-peptide sum that was of borderline significance ($P = 0.05$). Supplementary Fig. 1 shows the full breakdown of the distributions at the next visit.

We have performed proportional hazards regressions to examine associations of T1D with dysglycemia and with the DPTRS as single variables. Each was highly predictive of T1D when included alone ($P < 0.001$ for both). However, when both were included in a model, while T1D and the DPTRS were still strongly associated ($P < 0.001$), there was no longer a significant association between T1D and dysglycemia ($P = 0.783$).

Table 1 shows how the DPTRS could be used in prevention trials. Risk estimates

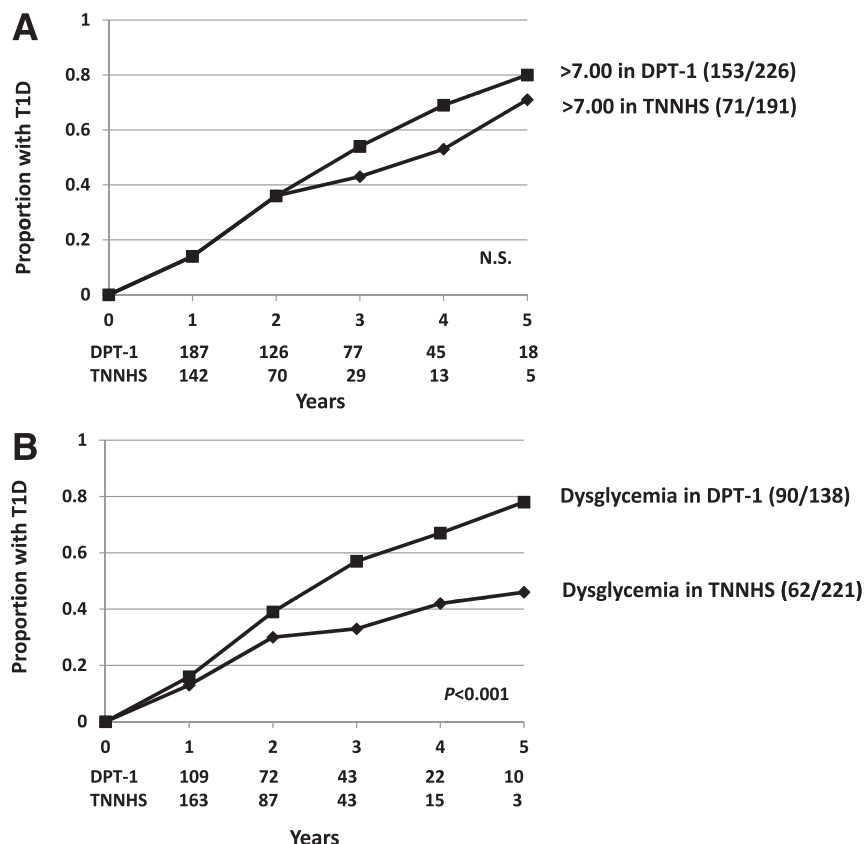


Figure 3—Shown are cumulative incidence curves of TNNHS and DPT-1 participants who either had DPTRS values >7.00 (A) or dysglycemia (B). Among those with DPTRS values >7.00, the cumulative incidence was similar between the TNNHS and DPT-1, whereas among those with dysglycemia, the cumulative incidence was markedly lower in the TNNHS than in DPT-1.

are indicated at 2, 3, and 4 years of follow-up for those above certain DPTRS thresholds at baseline in the TNNHS. Also shown are the risk estimates for dysglycemia. As the DPTRS thresholds increased, the risk estimates increased. If the DPTRS threshold of 7.00 was used instead of dysglycemia for the selection of prevention trial participants, more would have been diagnosed (71 vs. 62) with a smaller number entered (191 vs. 221). Other thresholds could be selected according to the desired number of participants and their level of

risk. For example, if the 6.75 threshold was chosen in place of dysglycemia for the selection of participants, appreciably greater numbers would have been entered (253 vs. 221) and diagnosed (85 vs. 62) even though the risk was still comparable.

We examined the occurrence of T1D for those above DPTRS thresholds when dysglycemia was absent and for those below DPTRS thresholds when dysglycemia was present (Supplementary Table 1). Whereas 22 of 64 (39%) were diagnosed of those

normoglycemic with a DPTRS value >7.00, only 13 of 94 (13%) were diagnosed of those dysglycemic with a DPTRS value <7.00.

CONCLUSIONS

The findings indicate that a reliance upon dysglycemia as a demarcation of risk in autoantibody-positive populations could result in a less-than-optimal classification of risk for prevention trials. The risk of certain individuals with normoglycemia could actually be higher than some with dysglycemia. The findings also show that the risk implications of dysglycemia can vary markedly according to the particular population that is studied. In addition, the presence of dysglycemia can be inconsistent when OGTTs are repeated in individuals. It appears that the use of the DPTRS could help to mitigate these limitations.

It is evident that the DPTRS can improve the accuracy of risk classification when it is used in conjunction with dysglycemia for prediction. However, the data in Table 1 suggest that it might be advantageous to use DPTRS thresholds in place of dysglycemia for prevention trials. In addition to improving accuracy, DPTRS thresholds provide a choice of target populations with different risks. If greater risk homogeneity is desired for a trial, bounded categories could be used. Risk estimates of specific DPTRS categories have previously been reported (8); these can be used for reference. The DPTRS provides selection from a risk continuum, whereas dysglycemia only offers a dichotomous selection.

The findings also indicate that the DPTRS effectively refines prediction by autoantibodies. The presence of multiple autoantibodies has been used as an indicator of higher risk for T1D.

Table 1—Risk estimates of T1D for dysglycemia and DPTRS thresholds at baseline in the TNNHS (n = 991)

	Total	Dysglycemia	Diagnosed	2-Year risk (with 95% CI)	3-Year risk (with 95% CI)	4-Year risk (with 95% CI)
Dysglycemia	221	—	62	0.30 (0.24–0.38)	0.33 (0.26–0.41)	0.42 (0.32–0.54)
DPTRS >6.50	344	151	95	0.27 (0.22–0.33)	0.35 (0.28–0.41)	0.42 (0.34–0.51)
DPTRS >6.75	253	143	85	0.33 (0.27–0.40)	0.41 (0.34–0.49)	0.51 (0.41–0.62)
DPTRS >7.00	191	127	71	0.36 (0.28–0.44)	0.43 (0.35–0.52)	0.53 (0.42–0.64)
DPTRS >7.25	146	110	62	0.43 (0.34–0.53)	0.50 (0.41–0.61)	0.59 (0.47–0.72)
DPTRS >7.50	109	93	50	0.49 (0.39–0.60)	0.56 (0.44–0.68)	0.62 (0.47–0.77)

However, those with DPTRS values <7.00 were at much lower risk than those with DPTRS values >7.00.

A recent article (12) examined prediction by an autoantibody risk score in TNNHS participants that takes both positivity and level into account. In that article, the area under the receiver operating characteristic curve was higher for the DPTRS than the autoantibody risk score. Also, when the autoantibody risk score and the DPTRS were both included in a regression model, the DPTRS was still highly predictive. The combination of the two risk scores yielded a more accurate prediction. Risk can vary substantially for a given number of autoantibodies, depending upon which specific autoantibodies are positive (13). It is likely that risk prediction will be improved further with the refinement of autoantibody prediction (14,15) and the integration of autoantibody and metabolic information.

The first-phase insulin response is predictive of T1D (16–19). However, it is relatively weak in comparison with other predictors, both overall (7) and among those with normoglycemia (6). Moreover, the performance of intravenous glucose tolerance testing is cumbersome for participants and labor intensive for staff.

Individuals with normoglycemia identified as being at substantial risk for T1D were much younger than those with dysglycemia. This finding suggests that the T1D risk of children can be particularly underestimated when dysglycemia is used as an indicator of risk and highlights the importance of the consideration of age in assessing the risk of T1D. The DPTRS is useful for identifying normoglycemic individuals at high risk in large part because it includes age, which is inversely related to the risk for T1D (7,8).

The lack of consistency in the cumulative incidence curves between the TNNHS and DPT-1 among those with dysglycemia shows that a dependence upon glucose indices alone for risk estimation can be misleading. The greater consistency of DPTRS values >7.00 is possibly attributable to the consideration of other factors associated with risk.

The frequent reversion from the dysglycemic state to the normoglycemic state in the TNNHS is consistent with previous findings in DPT-1 in which there were frequent fluctuations between states of glycemia during the progression to T1D (20). The lower reversion rate from DPTRS values >7.00 to <7.00 suggests that DPTRS thresholds are more reliable indicators of risk than dysglycemia.

A limitation of the study is that only autoantibody-positive individuals were studied. Thus, the findings are not necessarily generalizable to other populations, such as those at genetic risk for T1D. However, since DPT-1 participants were selected on the basis of autoantibodies that differ from those in the TNNHS, the findings show that the DPTRS has general utility for improving the risk classification of autoantibody-positive populations. Another potential limitation is that participants were informed of dysglycemic OGTTs. This could conceivably have increased the proportion reverting to normoglycemia. Although no treatment was recommended, it is possible that some could have undertaken treatment on their own.

Dysglycemia has been shown to be a frequent precursor to T1D (4,21), and an understanding of its development in the pathogenesis of diabetes is of importance. However, data now suggest that the prediction accuracy of T1D can be improved well beyond the predictive information provided by glycemia status. The findings indicate that the DPTRS can refine prediction and ultimately improve the accuracy of T1D risk classification.

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study and reviewed the manuscript. C.A.B. provided statistical support. D.C.B. provided programming and statistical support. D.C. provided programming and statistical support. G.E. conducted the study and reviewed the manuscript. J.P.P. conducted the study, reviewed the manuscript, and assisted in writing 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.

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