The Development and Utility of a Novel Scale That Quantifies the Glycemic Progression Toward Type 1 Diabetes Over 6 Months

OBJECTIVE
We developed a scale to serve as a potential end point for 6-month glycemic progression (PS6M) toward type 1 diabetes (T1D) in autoantibody-positive relatives of individuals with T1D.

RESEARCH DESIGN AND METHODS
The PS6M was developed from Diabetes Prevention Trial–Type 1 (DPT-1) data and tested in the TrialNet Pathway to Prevention Study (PTP). It is the difference between 6-month glucose sum values (30–120 min oral glucose tolerance test values) and values predicted for nonprogressors.

RESULTS
The PS6M predicted T1D in the PTP (P < 0.001). The area under the receiver operating characteristic curve was greater (P < 0.001) for the PS6M than for the baseline–to–6-month difference. PS6M values were higher in those with two or more autoantibodies, 30–0 min C-peptide values <2.00 ng/mL, or DPT-1 Risk Scores >7.00 (P < 0.001 for all).

CONCLUSIONS
The PS6M is an indicator of short-term glycemic progression to T1D that could be a useful tool for assessing preventive treatments and biomarkers.

RESEARCH DESIGN AND METHODS
Subjects
The Diabetes Prevention Trial–Type 1 (DPT-1) and the TrialNet Pathway to Prevention Study (PTP) have been described in detail (1,2,7). All participants were...
pancreatic autoantibody-positive relatives of patients with T1D. Those included in the analysis underwent a 2-h oral glucose tolerance test (OGTT) at baseline and within 6 ± 3 months from the baseline OGTT. Individuals diagnosed with T1D at or before the 6-month OGTT were excluded from the analysis. Both studies were approved by institutional review boards at all participating sites, and written informed consent or assent, as appropriate, was obtained in both studies.

Procedures
DPT-1 and PTP participants underwent 2-h OGTT surveillance at intervals of 6 ± 3 months. OGTTs were repeated for the diagnostic confirmation of T1D when fasting glucose values were ≥126 mg/dL and/or 2-h glucose values were ≥200 mg/dL if individuals were asymptomatic. Plasma glucose levels were measured by the glucose oxidase method. C-peptide was measured with the Tosoh assay (8).

Data Analysis
We have developed and tested a scale of glycomic progression to T1D by 1) characterizing the glycomic progression of DPT-1 nonprogressors, 2) using this as a basis for a scale measuring glycomic progression relative to that expected for nonprogressors, and 3) obtaining another scale based on PTP nonprogressors with the same method. These two scales were subsequently compared within the full PTP population of progressors and nonprogressors. The details are presented below.

Among nonprogressors to T1D followed for over 2 years after the 6-month visit in DPT-1 (median: 3.98 years; 25th percentile: 3.03 years; 75th percentile: 4.89 years), a linear regression equation was obtained for the association of the glucose sum (sum of glucose values at 30, 60, 90, and 120 min) at 6 months with the glucose sum at baseline. (Baseline and 6-month mean ± SD glucose sum values are reported in Supplementary Table 1.) The equation describing the association ($r = 0.59; n = 245$) was:

$$\text{predicted 6-month glucose sum for DPT-1 nonprogressors} = 204 + 0.599 \times \text{glucose sum at baseline}$$

That DPT-1 equation for nonprogressors was then used to develop a progression scale for 6 months (PS6M), as described by the following equation:

$$\text{PS6M} = \text{actual glucose sum at 6 months} - (204 + 0.599 \times \text{glucose sum at baseline for nonprogressors})$$

To assess whether the PS6M from DPT-1 could be used in other autoantibody-positive populations, we obtained a second linear regression equation ($r = 0.61; n = 397$) for the 6-month glucose sum of PTP nonprogressors:

$$\text{predicted 6-month glucose sum for PTP nonprogressors} = 187 + 0.632 \times \text{glucose sum at baseline}$$

The PS6MPTP is described by the following equation:

$$\text{PS6M}_{\text{PTP}} = \text{actual glucose sum at 6 months} - (187 + 0.632 \times \text{glucose sum at baseline for nonprogressors})$$

The $t$ test was used for comparisons between groups. Proportional hazards regression and Kaplan-Meier estimations were used to assess the occurrence of T1D. Areas under the receiver operating characteristic curves were also calculated. SAS 9.1.3 and 9.2 software was used for the analysis. Confidence intervals and $P$ values are two-sided, except for sample size estimations, which use one-sided $P$ values; TrialNet protocols are performed on the basis of one-sided $P$ values.

**RESULTS**

The analysis included 1,245 PTP participants (mean ± SD age: 18.2 ± 13.2 years; 47% male) with baseline and 6-month OGTTs. 

Applicability of PS6M for PTP Participants
The equation shown below describes the relationship in the full PTP cohort (progressors and nonprogressors) between progression scale values based on PTP nonprogressors (PS6M$_{\text{PTP}}$) and on DPT-1 nonprogressors (PS6M).

$$\text{PS6M}_{\text{PTP}} = -0.011 + 0.993 \times \text{PS6M}$$

The equation and the accompanying scatterplot (Supplementary Fig. 1) show that PS6M and PS6M$_{\text{PTP}}$ values were almost identical; the regression line essentially crossed the 0 mg/dL value. We used the PS6M in the analyses shown below for the PTP cohort because its development was independent of that cohort.

**Prediction of T1D**
The PS6M was a strong predictor of T1D among PTP participants. Proportional hazards regression showed a substantial overall association of the subsequent development of T1D with PS6M values ($\chi^2 = 178; P < 0.001$). The fourth quartile–to–first quartile hazard ratio (with 95% CIs) for T1D of the PS6M (7.12 [4.32, 11.72]; $P < 0.001$) was much greater ($P < 0.001$) than the fourth quartile–to–first quartile hazard ratio for T1D of the baseline–to–6-month difference (1.40 [1.22, 1.60]; $P < 0.001$). The area under the receiver operating characteristic curve (Supplementary Fig. 2) was also substantially greater ($P < 0.001$) for the PS6M (0.75 [0.71, 0.79]; $P < 0.001$) than for the baseline–to–6-month difference (0.64 [0.60, 0.69]; $P < 0.001$). The association of T1D with the PS6M was nonlinear (Fig. 1). The 3-year risk remained low for PS6M values <0 mg/dL and then increased appreciably, such that the 3-year risk exceeded 0.50 for PS6M values ≥100 mg/dL.

**Assessment of Associations With Biomarkers**
The PS6M was used to assess associations of 6-month glycomic progression with known T1D biomarkers. PS6M values were greater in PTP participants with two or more autoantibodies at baseline than in those with one autoantibody (28 ± 102 mg/dL [$n = 570$] vs. 6 ± 84 mg/dL [$n = 675$]; $P < 0.001$). PS6M values were also greater in participants with baseline 30–0 min C-peptide values <2.00 ng/mL than with values ≥2.00 ng/mL (43 ± 98 mg/dL [$n = 214$] vs. 11 ± 91 mg/dL [$n = 1,027$]; $P < 0.001$), and in participants with baseline DPT-1 Risk Score (9) values >7.00 than with values ≤7.00 (56 ± 119 mg/dL [$n = 256$] vs. 6 ± 82 mg/dL [$n = 989$]; $P < 0.001$).

**Potential Use in Short-term Prevention Trials**
With PS6M as an end point, a controlled trial of individuals with two or more autoantibodies (equal numbers, one-sided $P$ values with a significance of $P < 0.05$ and a power of 0.80 for a 50% reduction of those exceeding a PS6M threshold) could be performed with as few as 46 participants per group. Alternatively,
uncontrolled pilot studies can be performed. For example, to test (power = 0.80, one-sided \( \alpha \) value = 0.05) whether a potential treatment can lower the PS6M from a previously observed mean value of 30 mg/dL in a particular target population to the expected mean value for nonprogresors (i.e., 0 mg/dL), as few as 43 subjects (all on treatment) would be needed.

CONCLUSIONS
The applicability of the PS6M across autoantibody-positive populations, its prediction of T1D, and its associations with T1D biomarkers suggest that the PS6M can help to facilitate the evaluation of preventive treatments and biomarkers of T1D. The PS6M is uniquely suited for these purposes because it is indicative of the change in glycemia over a short, specified period of time. It was a far better predictor of T1D than the difference in glucose values between the OGTTs. The PS6M acts as a frame of reference for progression toward T1D because it is based on the expected 6-month glucose sum values of nonprogresors.

The PS6M could reduce numbers and the length of follow-up, and thus increase the feasibility for assessing multiple potential preventive treatments in early-phase clinical trials. It is conducive for performing uncontrolled pilot studies because the reduction of PS6M values toward the expected average value for nonprogresors (i.e., 0 mg/dL) could serve as an end point. Although highly predictive, the PS6M is not a diagnostic surrogate for T1D per se. Rather, it would indicate the effect of an intervention on the glycemic progression toward T1D.

The higher PS6M values among those with multiple autoantibodies, low 30–0 min C-peptide values, or high DPT-1 Risk Score values indicate that the PS6M can also be used to assess the influence of biomarkers upon short-term changes in glycemia. As new biomarkers are discovered, there is a need to examine how they relate to changes in glycemia during the progression to T1D.

Because the PS6M was developed in autoantibody-positive relatives of patients with T1D, its use should be restricted to those populations. Moreover, although the PS6M was developed in DPT-1 and tested in the PTP, its applicability in other autoantibody-positive populations is not a certainty.

There are no prior reports of changes in glycemia during a 6-month period for use as an end point. Changes in HbA1C and C-peptide during a 2-year period have previously been assessed as possible end points (10).

In conclusion, as an indicator of short-term glycemic progression toward T1D, the PS6M provides a potentially useful tool for assessing preventive treatments and biomarkers of T1D.

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References
1. 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
2. Skyler JS, Krisher 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;28:1066–1076
3. Gale EA, Bingley PJ, Emmett CL, Collier T; European Nicotinamide Diabetes Intervention Trial (ENDIT) Group. European Nicotinamide Diabetes Intervention Trial (ENDIT): a randomised controlled trial of intervention before the onset of type 1 diabetes. Lancet 2004;363:925–931
4. 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;29:640–649
5. 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
6. Sosenko JM, Palmer JP, Rafkin-Mervis L, et al. Glucose and C-peptide changes in the perisonset period of type 1 diabetes in the Diabetes Prevention Trial—Type 1. Diabetes Care 2008;31:2189–2192
7. 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
8. Little RR, Rohlfing CL, Tennill AL, et al. Standardization of C-peptide measurements. Clin Chem 2008;54:1023–1026
9. Sosenko JM, Skyler JS, Mahon J, et al.; TrialNet and Diabetes Prevention Trial—Type 1 Study Groups. Validation of the Diabetes Prevention Trial—Type 1 Risk Score (DPTRS) in the TrialNet Natural History Study. Diabetes Care 2011;34:1785–1787
10. Krisher JP; Type 1 Diabetes TrialNet Study Group. The use of intermediate endpoints in the design of type 1 diabetes prevention trials. Diabetologia 2013;56:1919–1924