Slowed Metabolic Decline After 1 Year of Oral Insulin Treatment Among Individuals at High Risk for Type 1 Diabetes in the Diabetes Prevention Trial–Type 1 (DPT-1) and TrialNet Oral Insulin Prevention Trials

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We assessed whether oral insulin slowed metabolic decline after 1 year of treatment in individuals at high risk for type 1 diabetes. Two oral insulin trials that did not show efficacy overall and had type 1 diabetes as the primary end point were analyzed: the Diabetes Prevention Trial–Type 1 (DPT-1) and the TrialNet oral insulin trials. Oral glucose tolerance tests at baseline and after 1 year of treatment were analyzed. Among those at high risk (with a Diabetes Prevention Trial–Type 1 Risk Score [DPTRS] ≥6.75), the area under the curve (AUC) C-peptide increased significantly from baseline to 1 year in each oral insulin group, whereas the AUC glucose increased significantly in each placebo group. At 1 year, the AUC C-peptide/AUC glucose (AUC Ratio) was significantly higher in the oral insulin group than in the placebo group in each trial ($P <$ 0.05; $P = 0.057$ when adjusted for age in the TrialNet trial) and in both trials combined ($P < 0.01$ with or without adjustment for age). For a DPTRS <6.75, oral insulin groups did not differ from placebo groups in the AUC Ratio. The findings suggest that 1 year of treatment with oral insulin slows metabolic deterioration in individuals at high risk for type 1 diabetes. Moreover, the findings further suggest that metabolic end points can be useful adjuncts to the diagnostic end point in assessments of preventive treatments for the disorder.

Two randomized placebo-controlled trials have been performed to assess whether oral insulin can delay progression to type 1 diabetes in autoantibody-positive relatives of patients with type 1 diabetes (1,2). In the Diabetes Prevention Trial–Type 1 (DPT-1), there was no overall effect of oral insulin. However, in a subgroup of participants with insulin autoantibody (IAA) titers ≥80, there was a lower occurrence of type 1 diabetes among those receiving oral insulin. The subsequent TrialNet trial included individuals who had autoantibody patterns with a risk equivalent to those with the higher IAA titers in the DPT-1 oral insulin trial. Despite the lack of an overall effect, oral insulin decreased progression to diabetes in a prespecified secondary stratum with lower first-phase insulin responses (FPIRs).

The seemingly greater responses to oral insulin among groups with high IAA titers and low FPIR suggested that treatment responsiveness could be related to a higher risk for type 1 diabetes. Moreover, in a recent trial of high-risk individuals, the time to diagnosis was delayed in those receiving teplizumab (3). Thus, we analyzed the DPT-1 and the TrialNet oral insulin trials to assess whether oral insulin slowed metabolic decline in high-risk individuals.

RESEARCH DESIGN AND METHODS

Subjects
The DPT-1 oral insulin trial has been described previously (1). All participants were islet cell autoantibody– and IAA-positive relatives of individuals with type 1 diabetes. Those

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with dysglycemia or a low FPIR were excluded. These criteria were chosen so that the oral insulin trial cohort would have a 5-year risk of developing type 1 diabetes of 25–50%. In the TrialNet oral insulin trial (2), eligible individuals were required to fulfill the following autoantibody criteria: positivity for microinsulin autoantibodies in two samples; and either islet cell autoantibodies confirmed in two samples or, if not confirmed, GAD and insulinoma-associated antigen-2 autoantibody positivity in the same sample with at least one of those autoantibodies also positive in a different sample. These criteria were based on a post hoc analysis of the DPT-1 oral insulin trial, suggesting that among participants with IAA titers ≥80, those receiving oral insulin seemed to have a delayed time to diagnosis. The metabolic entry criteria were the same as those for the oral insulin trial. Data from participants in the DPT-1 and the TrialNet oral insulin trials who had undergone oral glucose tolerance tests (OGTTs) after a specified treatment duration approximating 1.00 year (0.75–1.25 years) were included in the analyses (described below): 76% (282 of 372) in the DPT-1 oral insulin trial and 89% (340 of 382) in the TrialNet oral insulin trial. There were no significant differences in any of the baseline characteristics between those included in and those excluded from the analyses for either trial (Supplementary Tables 1 and 2).

Procedures

In both the DPT-1 and the TrialNet oral insulin trials, participants were randomized to receive orally each day 7.5 mg of recombinant human insulin crystals (Eli Lilly) or placebo. Participants underwent 2-h OGTTs at 6-month intervals for the diagnostic surveillance of type 1 diabetes. Glucose and C-peptide were measured while participants were in a fasted state and at 30, 60, 90, and 120 min during the OGTT. Glucose was administered according to weight (1.75 g/kg) with a 75-g maximum. A type 1 diabetes diagnosis was based on American Diabetes Association criteria (1,2). Plasma glucose levels were measured by the glucose oxidase method. C-peptide was measured with the Tosoh assay. Autoantibody measurements were performed as previously described (1,2).

Statistical Analysis

The rationale for the timing of the end point was to maximize treatment duration without the potential bias of a high frequency of diagnoses prior to the visit. Given this rationale, the 1-year end point was specifically selected due to the sizable increase in the frequency of diagnoses from the 1-year visit to the 1.5-year visit. For example, in the DPT-1 oral insulin trial, among those with a Diabetes Prevention Trial–Type 1 Risk Score (DPTRS) ≥6.75, 6 (5 in the placebo group) were diagnosed before the 1-year visit, whereas 14 (11 in the placebo group) were diagnosed before the 1.5-year visit. The DPTRS was calculated as previously described (4) (see Supplementary Material). For metabolic end point comparisons, covariance

analyses were used with adjustments for baseline values, and with adjustments for age and the DPTRS.

Combined glucose and C-peptide (Glu-Cpep) response curves were derived from mean 30- to 120-min OGTT values for glucose and C-peptide plotted on a two-dimensional grid (glucose on the y-axis, C-peptide on the x-axis). Glu-Cpep response curve locations on the grid and shapes were compared. These locations and shapes change characteristically during the progression to type 1 diabetes. Centroids (central points) of the shapes of the Glu-Cpep response curves were calculated according to the formula for centroids of triangles (the curve shapes tended to be triangular). Glucose and C-peptide centroid coordinates indicate OGTT locations during progression. The ratio of these coordinates correlates very highly with the area under the curve (AUC) C-peptide/AUC glucose (AUC Ratio). Student t tests and χ^2 tests were used to assess differences. Cox regression was used for generating hazard ratios (HRs) and for making adjustments when type 1 diabetes was an end point. Because the overall follow-up was longer in the TrialNet oral insulin trial, its maximum was limited to 7.0 years for this analysis. Two-sided P values were used to assess statistical significance. The analyses were performed with SAS, version 9.4. A DPTRS threshold ≥6.75 was chosen to define high risk, since the 3-year risk increases markedly as DPTRS values increase above 6.75 (5).

Data and Resource Availability

All TrialNet data generated or analyzed during this study can be requested from the National Institute of Diabetes and Digestive and Kidney Diseases Central Repository at https://repository.niddk.nih.gov/studies/trialnet/.

The resource generated and analyzed during this study is available from the corresponding author upon reasonable request.

RESULTS

Of the 282 participants from the DPT-1 oral insulin trial analyzed here, 90 (32%) had a DPTRS ≥6.75, whereas of the 340 from TrialNet, 118 (35%) had a DPTRS above that threshold (for a total of 208 participants with a DPTRS ≥6.75). Estimated 3-year risks were 56% for the high-risk group from DPT-1 and 55% for the high-risk group from TrialNet.

Figure 1 shows AUC C-peptide and AUC glucose changes in the high-risk groups of both trials from baseline to 1 year on a two-dimensional grid with glucose on the y-axis and C-peptide on the x-axis. Vectors representing changes on the grid differed in directionality between oral insulin and placebo groups in both trials. This was reflected by significant AUC C-peptide increases in oral insulin treatment groups of each trial (DPT-1: 3.28 ± 0.17 to 3.86 ± 0.21 ng/mL, $P = 0.002$ [$n = 37$]; TrialNet: 3.84 ± 1.51 to 4.20 ± 1.65 ng/mL, $P = 0.018$ [$n = 60$]), and significant increases of AUC glucose in placebo groups of each trial (DPT-1: 132.7 ± 13.8 to 148.7 ± 43.2 mg/dL, $P = 0.006$ [$n = 53$]; TrialNet: 132.9 ± 13.5 to 146.4 ± 28.9 mg/dL,
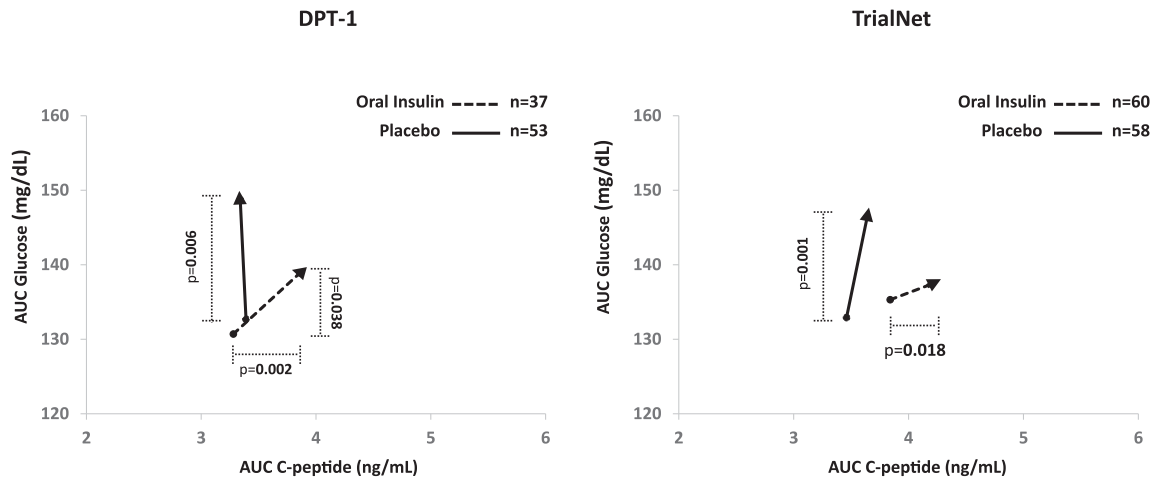
DPT-1

TrialNet

Figure 1—Concurrent changes of mean AUC glucose and mean AUC C-peptide values from the baseline OGTT (closed circles) to the 1-year OGTT (arrows). P values are included only for significant changes in AUC glucose or AUC C-peptide. In both DPT-1 and TrialNet, the placebo groups had significant increases in AUC glucose, whereas the oral insulin groups had significant increases in AUC C-peptide. There was also a significant increase in the AUC glucose in the DPT-1 oral insulin group, though not to the extent that occurred in the placebo group. Note the similarities between the two trials in the directionality of the changes.

$P = 0.001$ [$n = 58$]). AUC glucose increased significantly in the DPT-1 oral insulin group (130.7 ± 14.2 to 138.9 ± 26.0 mg/dL, $P = 0.038$), but to a lesser extent than in the placebo group.

Figure 2 shows comparisons between oral insulin and placebo groups at 1 year for the AUC Ratio (adjusted for baseline) among those at high risk (see Supplementary Table 3 for values). The AUC Ratio was higher in oral insulin groups ($P < 0.05$) of both trials. Since those taking oral insulin tended to be older with lower DPTRS values (Supplementary Tables 4 and 5), adjustments were made for age and for the DPTRS. Differences remained significant except for some confounding by age in the TrialNet comparison ($P = 0.057$). Among those with a DPTRS <6.75 (192 participants in DPT-1 and 222 in TrialNet), AUC Ratio values did not differ between the oral insulin and placebo groups.

Similar 1-year outcomes between the trials is evident in Fig. 3, which shows Glu-Cpep response curves derived from mean 30- to 120-min values of glucose and C-peptide from the OGTTs of each trial, plotted on a two-dimensional grid (glucose on y-axis; C-peptide on x-axis). Shapes of Glu-Cpep response curves were quite similar between the two placebo groups (Fig. 3A) and also between the two oral insulin groups (Fig. 3B), whereas shapes of the response curves differed appreciably between placebo and oral insulin groups in both trials.

We also compared the oral insulin and placebo groups after combining the high-risk participants from the two trials ($n = 208$). (There were no significant interactions between trial and treatment.) The AUC Ratio was significantly higher in the oral insulin group (2.99 ± 1.10) than in the placebo group (2.50 ± 0.99), which persisted after adjustments for age and for the DPTRS ($P < 0.01$).

Figure 4 shows shapes of Glu-Cpep response curves at 1 year with the two oral insulin groups combined and with

the two placebo groups combined. Response curve shapes are included for values from a DPT-1 reference group of 151 participants who were within 0.50 ± 0.25 years before diagnosis. A central point (centroid) for each Glu-Cpep response curve shape was added to the figure to indicate the location on the grid. The placebo group had response curves more like those of the reference group than did the oral insulin group, with regard to both shape and the location of the centroid on the grid.

We compared oral insulin and placebo groups for the primary end point of the original trials: a diagnosis of type 1 diabetes. The hazard ratio (HR) suggested a protective effect of oral insulin in DPT-1 (HR 0.494 [95% CI 0.255, 0.955], $P = 0.036$). The P values adjusted for age and the DPTRS were 0.039 and 0.052, respectively. However, in TrialNet, there was a nonsignificant trend (HR 0.696 [95% CI 0.431, 1.22], $P = 0.137$).

We combined the high-risk participants from the trials to compare the oral insulin and placebo groups for the type 1 diabetes end point. In that analysis, the HR suggested a protective effect of oral insulin (HR 0.604 [95% CI 0.412, 0.885], $P = 0.010$), which was significant after adjustment for age ($P = 0.010$) and the DPTRS ($P = 0.014$).

DISCUSSION

The findings suggest that oral insulin slows metabolic progression in high-risk individuals. This suggestion is based on analyses showing a higher 1-year AUC Ratio in oral insulin groups than in placebo groups of both oral insulin trials, with corroborating evidence from OGTT vectors for the degree of progression and OGTT phenotypes.

The diagnosis of type 1 diabetes was delayed in the high-risk participants receiving oral insulin in DPT-1, but only a trend was apparent for those in TrialNet. Although
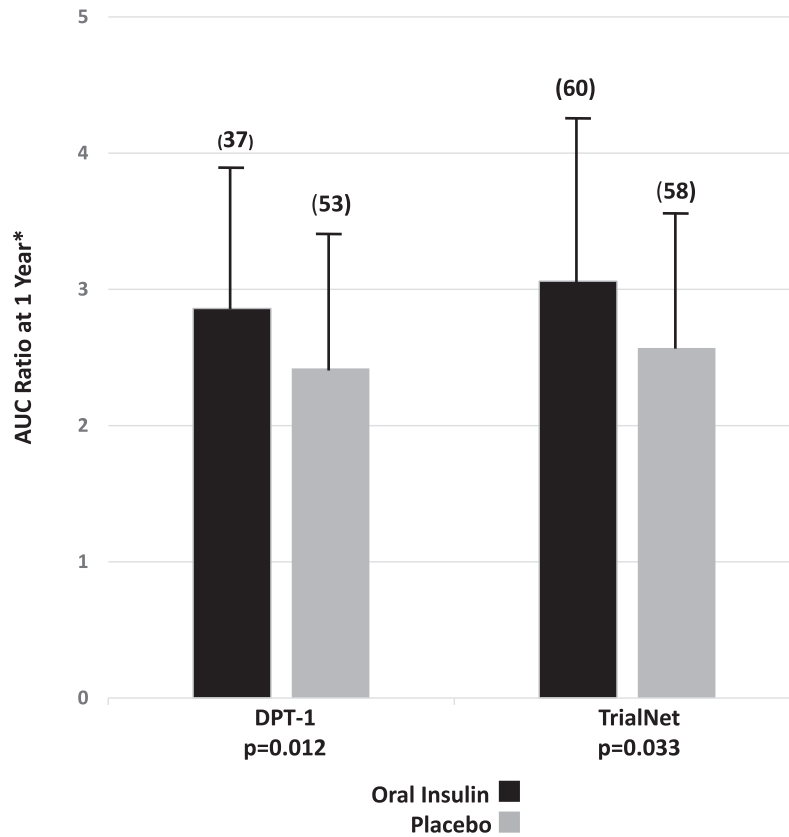
Figure 2—Mean and SD values of the AUC Ratio at the 1-year OGTT for the placebo and oral insulin groups among those at high risk for type 1 diabetes (DPTRS ≥6.75) in the DPT-1 and the TrialNet trials. Comparisons suggest an effect of oral insulin among those at high risk in both trials. The numbers of subjects are set in parentheses above the error bars. *(AUC C-peptide [ng/mL]/AUC glucose [mg/dL]) × 100.

a diagnosis has been the gold standard for prevention trial end points, there are downsides to its use. Participants' adherence to taking study medication could decline as lengthy trials progress, resulting in diminished responsiveness to an experimental treatment (2). Also,

a diagnostic end point can be insufficient for assessing timing and sustainability of treatment efficacy and for understanding mechanisms of treatment effects. Intermediate metabolic end points could be helpful for such assessments and also for reducing trial length, burden,
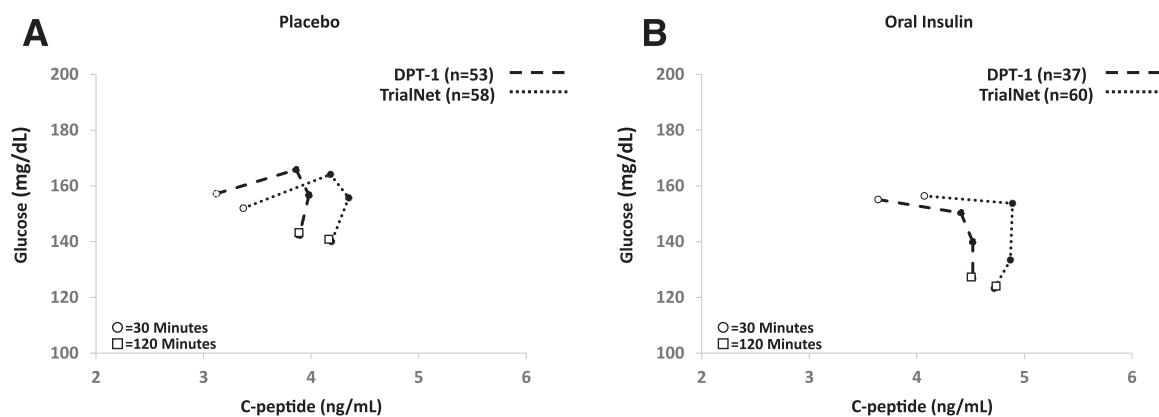

Figure 3—One-year Glu-Cpep response curves from concurrent mean glucose and mean C-peptide values at 30 (open circles), 60, 90, and 120 min (open squares) for those at high risk of developing type 1 diabetes (DPTRS ≥6.75) in the placebo and oral insulin groups of the two trials. Note the appreciable similarity at 1 year of the Glu-Cpep response curve shapes in the two placebo groups (A) and the similarity of the Glu-Cpep response curve shapes in the two oral insulin groups (B). Also, note the similarity of the trials for the differences between the placebo Glu-Cpep response curve shapes and the oral insulin Glu-Cpep response curve shapes.
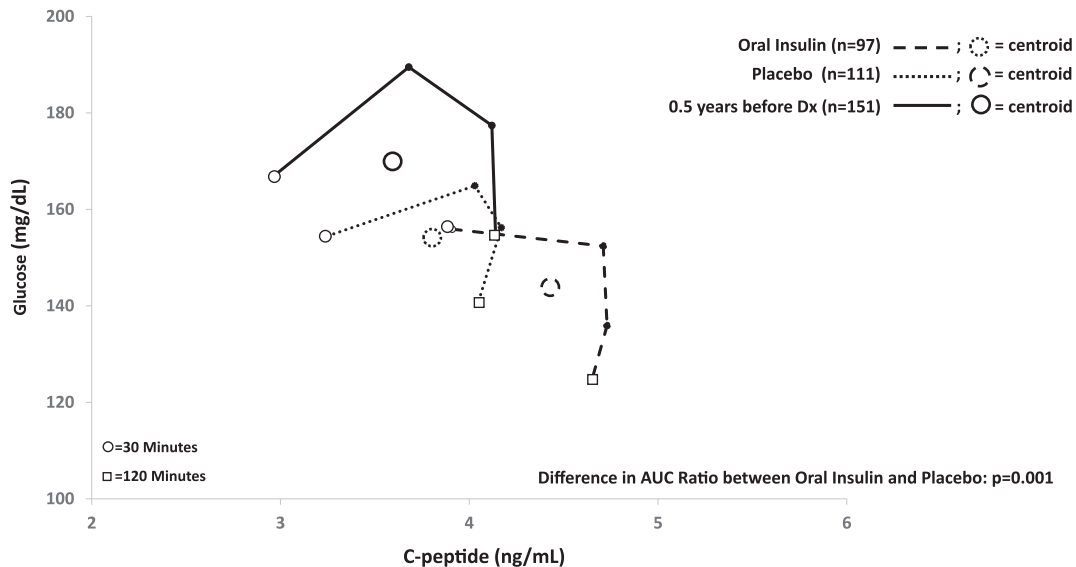
Figure 4—One-year Glu-Cpep response curves of mean glucose and mean C-peptide values at 30 (open circles), 60, 90, and 120 min (open squares) from the oral insulin and placebo groups after the trials were combined. Central points (centroids) of the Glu-Cpep response curves from the oral insulin and placebo groups are included. Also included is the Glu-Cpep response curve and its centroid from OGTTs of a reference group of DPT-1 participants within 0.50 ± 0.25 years before diagnosis. Note that the placebo Glu-Cpep response curve centroid is more proximal to the Glu-Cpep response curve centroid of those about to be diagnosed than the oral insulin Glu-Cpep response curve centroid. Additionally, the shape of the placebo Glu-Cpep response curve is more similar to that of the prediagnostic Glu-Cpep response curve (reference group). Dx, diagnosis.

and costs. However, although the findings from this study should encourage the development of metabolic end points, they would be adjuncts to the diagnosis end point.

A DPTRS ≥ 6.75 defines an advanced metabolic stage at which oral insulin seems to be effective. Since evidence suggests that the loss of β-cell function begins to accelerate ~ 1–2 years prior to diagnosis (6–8), oral insulin could possibly interfere with factors(s) contributing to that acceleration in high-risk individuals.

There is little prior information regarding metabolic measures as type 1 diabetes prevention trial end points. One study examined changes in HbA$_{1c}$, glucose, and C-peptide measures over 2 years and concluded that such measures have potential as intermediate end points (9).

This study's main limitation was the post hoc analysis. Since such analyses have potential for bias, they should be interpreted cautiously. In particular, exclusions due to absent 1-year OGTTs could have introduced a bias. However, there were no significant differences between those included in and those excluded from the analyses. The study's main strength was the ability to assess the consistency of findings between two independent oral insulin trials.

The findings raise the question of whether higher doses of oral insulin would have yielded a larger and more general benefit for the full cohort. Evidence suggests that oral insulin at doses higher than the 7.5 mg used in the trials has a more favorable effect on the immune system (10).

In conclusion, although the findings cannot be considered definitive, they seem sufficiently promising to warrant continuing assessments of oral insulin as a potential preventive treatment for type 1 diabetes. In addition, it seems that intermediate metabolic end points could help to substantially shorten prevention trials and facilitate the evaluation of preventive treatments for type 1 diabetes.

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References
1. 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
2. Writing Committee for the Type 1 Diabetes TrialNet Oral Insulin Study Group; Krischer JP, Schatz DA, Bundy B, Skyler JS, Greenbaum CJ. Effect of oral insulin on prevention of diabetes in relatives of patients with type 1 diabetes: a randomized clinical trial. JAMA 2017;318:1891–1902
3. Herold KC, Bundy BN, Long SA, et al.; Type 1 Diabetes TrialNet Study Group. An anti-CD3 antibody, teplizumab, in relatives at risk for type 1 diabetes. N Engl J Med 2019;381:603–613

4. Sosenko JM, Skyler JS, Mahon J, et al.; Type 1 Diabetes TrialNet and Diabetes Prevention Trial-Type 1 Study Groups. Use of the Diabetes Prevention Trial-Type 1 Risk Score (DPTRS) for improving the accuracy of the risk classification of type 1 diabetes. Diabetes Care 2014;37:979–984

5. 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 in the TrialNet Natural History Study. Diabetes Care 2011;34:1785–1787

6. 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

7. Ferrannini E, Mari A, Nofrate V, Sosenko JM, Skyler JS; DPT-1 Study Group. Progression to diabetes in relatives of type 1 diabetic patients: mechanisms and mode of onset. Diabetes 2010;59:679–685

8. Evans-Molina C, Sims EK, DiMeglio LA, et al.; Type 1 Diabetes TrialNet Study Group. β Cell dysfunction exists more than 5 years before type 1 diabetes diagnosis. JCI Insight 2018;3:e120877

9. Krischer 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

10. Bonifacio E, Ziegler AG, Klingensmith G, et al.; Pre-POINT Study Group. Effects of high-dose oral insulin on immune responses in children at high risk for type 1 diabetes: the Pre-POINT randomized clinical trial. JAMA 2015;313:1541–1549