Fall in C-Peptide During First 4 Years From Diagnosis of Type 1 Diabetes: Variable Relation to Age, HbA_{1c}, and Insulin Dose

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OBJECTIVE

We aimed to describe the natural history of residual insulin secretion in Type 1 Diabetes TrialNet participants over 4 years from diagnosis and relate this to previously reported alternative clinical measures reflecting β-cell secretory function.

RESEARCH DESIGN AND METHODS

Data from 407 subjects from 5 TrialNet intervention studies were analyzed. All subjects had baseline stimulated C-peptide values of ≥0.2 nmol/L from mixed-meal tolerance tests (MMTTs). During semiannual visits, C-peptide values from MMTTs, HbA_{1c}, and insulin doses were obtained.

RESULTS

The percentage of individuals with stimulated C-peptide of ≥0.2 nmol/L or detectable C-peptide of ≥0.017 nmol/L continued to diminish over 4 years; this was markedly influenced by age. At 4 years, only 5% maintained their baseline C-peptide secretion. The expected inverse relationships between C-peptide and HbA_{1c} or insulin doses varied over time and with age. Combined clinical variables, such as insulin-dose adjusted HbA_{1c} (IDAA1C) and the relationship of IDAA1C to C-peptide, also were influenced by age and time from diagnosis. Models using these clinical measures did not fully predict C-peptide responses. IDAA1C ≤9 underestimated the number of individuals with stimulated C-peptide ≥0.2 nmol/L, especially in children.

CONCLUSIONS

Current trials of disease-modifying therapy for type 1 diabetes should continue to use C-peptide as a primary end point of β-cell secretory function. Longer duration of follow-up is likely to provide stronger evidence of the effect of disease-modifying therapy on preservation of β-cell function.

Type 1 Diabetes TrialNet is an international network established to conduct clinical trials to intervene in the type 1 diabetes disease process (1), either before diagnosis (prevention) or after clinical diagnosis (intervention), with the aim of preserving β-cell function.

Clinical trials to alter the course of β-cell destruction after diagnosis usually consider the amount of residual insulin secretion after 1 or 2 years of therapy as the primary outcome measure to assess effectiveness. Although other assessments have been used, insulin secretion is generally measured through stimulated

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**A complete list of the Type 1 Diabetes TrialNet Study Group can be found in the Supplementary Data online.*

C-peptide from a mixed-meal tolerance test (MMTT). These approaches follow recommendations published in (2,3) and echoed by regulatory agencies as appropriate end points.

Nonetheless, there have been discussions that end points more directly linked to clinical parameters are also important. The European Medicines Agency and the U.S. Food and Drug Administration have both recommend considering glycemic control and insulin doses used. Specific mention has been the use of insulin dose-adjusted HbA_{1c} (IDAA1C) (calculated as HbA_{1c} [%] + 4 × insulin dose [units/kg/24 h]) ≤9 as a definition of partial remission (4). Similarly, a composite end point of insulin dose of ≤0.5 units/kg/day and HbA_{1c} ≤6.5% was recently used as the primary end point in a phase III study evaluating teplizumab in recently diagnosed individuals (5). This trial failed to demonstrate therapeutic effectiveness with this end point, despite robust results from other randomized but not placebo-controlled trials of the same agent using MMTT C-peptide as the primary end point.

Since early 2000, Type 1 Diabetes TrialNet has conducted five interventional clinical trials aiming to alter the course of β-cell destruction (6–10). We thus examined the data set from these studies to explore the relationship of insulin use, glycemic control, and MMTT C-peptide over time.

RESEARCH DESIGN AND METHODS

Subjects

Data from 407 subjects were included in this analysis. They included all subjects from three studies in which the tested intervention had no significant effect on β-cell function (6,7,9) as well as subjects in placebo arms only from two other studies (8,10). Demographic and baseline characteristics are reported in Supplementary Table 1. All subjects or their parents gave written informed consent and assent as appropriate before study participation. Entry criteria for all studies included a requirement for peak stimulated C-peptide by MMTT of ≥0.2 nmol/L, positivity for at least one diabetes-related islet autoantibody, and type 1 diabetes diagnosis within 100 days of randomization. The age range varied according to the study, collectively spanning ages 3–45 years. Subjects were monitored for up to 4 years after randomization with regularly scheduled MMTTs, as previously described. Subjects were monitored for the first 2 years under their original study protocol. Subsequently, subjects were enrolled in the TrialNet Long Term Investigative Follow-up (LIFT) protocol and monitored regularly with MMTT assessments as long as C-peptide was present.

MMTT

As previously described (2), data were collected from a 2-h MMTT begun before 10:00 A.M. after an overnight fast. MMTTs were begun only if the fasting glucose levels were between 70 and 200 mg/dL. Boost-HP (Nestle Health Care Nutrition, Inc.) was used at a dose of 6 mg/kg to a maximum of 360 mL.

C-peptide and HbA_{1c} were measured in Northwest Lipid Laboratories at the University of Washington (Seattle, WA). C-peptide was measured by using a two-site immunoenzymometric assay performed on a Tosoh II 600 autoanalyzer. Samples with C-peptide ≥0.017 nmol/L were considered detectable. The C-peptide area under curve (AUC) was calculated using the trapezoidal method and then divided by the time period of the test. Insulin use was determined by averaging self-reported doses during a 3-day period the week before each MMTT visit.

Maintenance of C-Peptide

Subjects were classified as having maintained C-peptide over time if there was no change from baseline to each of the time points after baseline. To account for statistical variation in C-peptide measurements, we used three definitions of maintained C-peptide that are suggested by two published studies (2,11). The three definitions are similar in that they each consider no change or an increase from baseline to represent a positive response. They differ in the amount of decrease they allow for a subject to still be classified as having maintained C-peptide:

1. "Percentage change" definition: Follow-up C-peptide value of no more than 7.5% below baseline (one-half of the interassay coefficient of variation [CV] of the C-peptide assay used in the study) (11).
2. "Intertest Variability" definition: Change from baseline, either nonnegative or if negative, no more than 1 intertest SD bellow baseline (2).
3. "CV" definition: Change from baseline, either nonnegative or if negative, within the median CV from the MMTT/glucagon stimulation test study (2).

Statistical Analysis

Subjects were divided into one of three prespecified age cohorts based on age at time of randomization: < 12 years, 12–17 years, and ≥18 years. Associations between the covariates and the C-peptide AUC and C-peptide peak were assessed using Spearman correlation coefficients for continuous factors and ANOVA for categorical factors. C-peptide AUCs were calculated using the trapezoidal method; areas were then divided by the time period of the test (120 min). Kaplan-Meier analyses were used to assess time to C-peptide ≤0.20 nmol/L and time to undetectable C-peptide (≤0.017 nmol/L) across the period of 0 to 48 months. Simple least-squares regressions adjusted for baseline C-peptide were used to assess relationships between C-peptide and various factors. Similar analyses were used to assess the relationship between HbA_{1c} and various factors, adjusting for baseline HbA_{1c}. A significance of 0.05 was used in all tests. Adjustments were not made for multiple testing. SAS software was used for all analyses.

Because the analyses combined data from placebo-treated subjects from all studies with data from actively treated subjects from "negative" TrialNet intervention studies to increase the number of observations, we first investigated whether inclusion of the actively treated subjects affected the multivariate analyses by using a variable to indicate treatment in the active studies. The results were not significant at 0.05. The Levene test for homogeneity of variance and graphical comparisons were used to assess the appropriateness of combining the five studies into one analysis. The test was not significant (P = 0.67), and the graphical comparisons did not uncover any appreciable differences in variability.

RESULTS

C-Peptide Change Over Time

Demographic and baseline characteristics of the 407 subjects included in this analysis are reported in Supplementary Table 1. Overall, 84%, 63%, 41%, and

31% of individuals had peak stimulated C-peptide values ≥0.2 nmol/L at the end of 1, 2, 3, and 4 years of follow-up, respectively. The corresponding percentages of individuals with detectable stimulated C-peptide values (≥0.017 nmol/L) over time were 98%, 92%, 83%, and 69% at 1, 2, 3, and 4 years (Supplementary Fig. 1). The percentages differed markedly by age, as shown in Fig. 1.

We then evaluated C-peptide preservation over time, using the classification of subsets as having maintained C-peptide or not, separately for each of the three definitions introduced in the RESEARCH DESIGN AND METHODS. When the baseline was compared with year 1, 2, 3, and 4 values, 78 (21%), 37 (12%), 7 (6%), and 3 (5%) subjects maintained C-peptide as defined by the CV definition, respectively, with similar values for other definitions (as reported in Supplementary Table 2).

Relationship of C-Peptide With Clinical Variables HbA_{1c} and Insulin Use Varies by Age and Over Time

We evaluated the C-peptide (mean AUC) and the relationship of C-peptide with HbA_{1c} and insulin use over time by age category. As expected, mean C-peptide

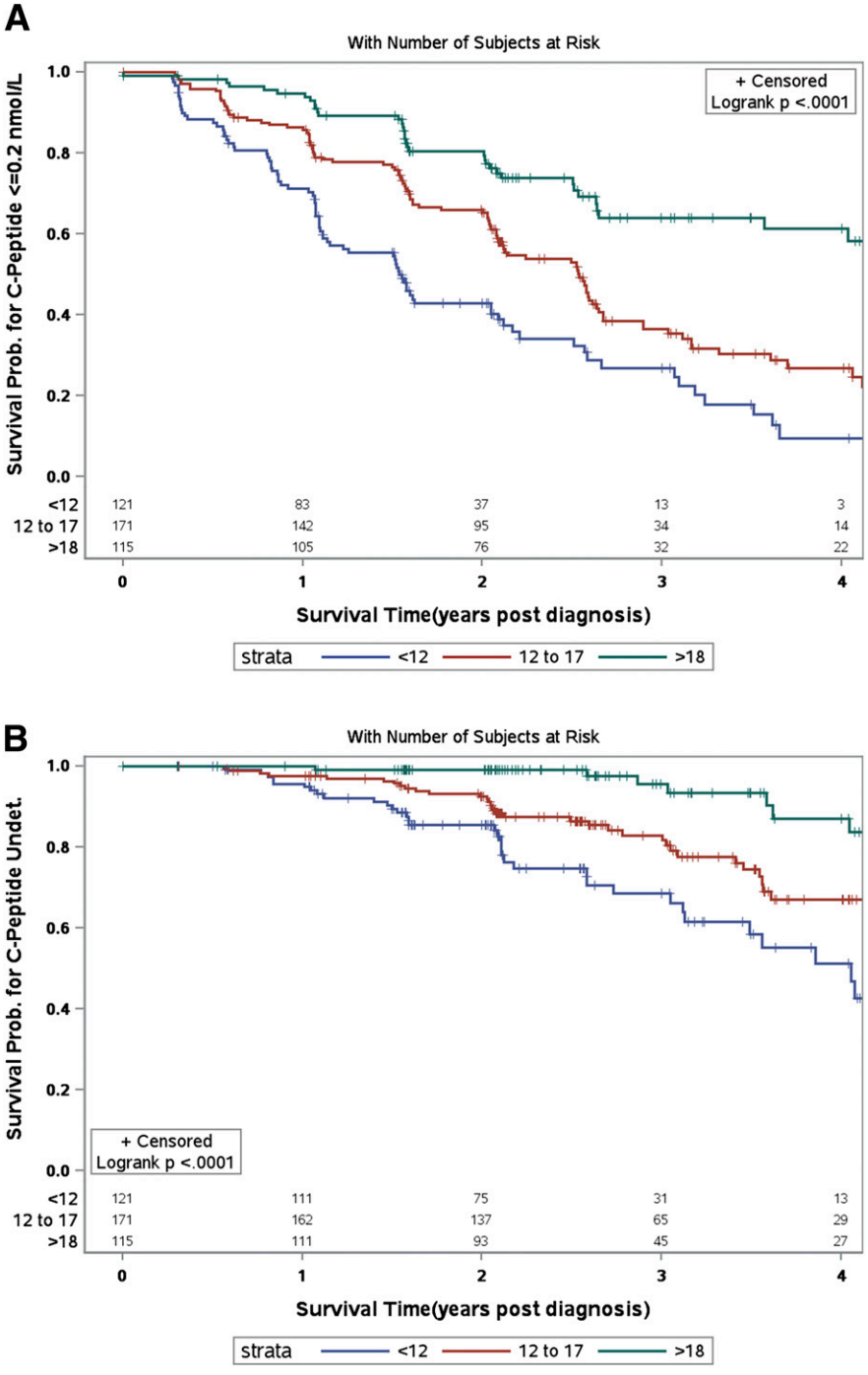

Figure 1—Probabilities (Prob.) of subjects having peak stimulated C-peptide ≤0.2 nmol/L (*A*) and undetectable (Undet.) stimulated C-peptide (*B*) over time by age. Subjects were divided into three predefined age-groups (<12, 12–17, and ≥18 years). C-peptide diminished over the 4 years from diagnosis and was affected by age.

values decreased in all age-groups over 4 years (Fig. 2*A*), although the rate of fall was less in adults. The relationship between C-peptide and HbA_{1c} (Fig. 2*B*) or insulin use in units/kg (Fig. 2*C*) also differed by age. The relationship between C-peptide and the clinical variables of HbA_{1c} and insulin use changed over time in all three age-groups.

To further explore relationships of clinical factors with C-peptide over time, we evaluated regression models using age as a continuous and categorical (data not shown) variable (age <18 or >18), sex, HbA_{1c}, insulin dose, and baseline stimulated C-peptide (0 months). Two points are noteworthy from this analysis. At each time period, the R^2 for these models ranged from 0.44 to 0.58, indicating that the above factors do not fully explain C-peptide concentrations (Table 1). Moreover, the effect of age, HbA_{1c}, insulin dose, and baseline stimulated C-peptide on the outcome varied over time, with only baseline C-peptide and HbA_{1c} remaining significantly associated with stimulated C-peptide at 4 years. Similarly, regression models including age, C-peptide, insulin dose, and HbA_{1c} at baseline had very weak ability to predict HbA_{1c} (R^2 from 0.16 to 0.33) at any time point (Table 1).

Relationship of C-Peptide and IDAA1C Over Time and by Age

IDAA1C $\leq$9 has been reported as indicative of "remission" (4). We first examined the effect of age and time on IDAA1C. As shown in Fig. 3, less than 80% of individuals met this definition at baseline, and by 2 years, less than 10% of children and 50% of adults remained with IDAA1C $\leq$9. We then explored the correlation between stimulated C-peptide and IDAA1C over time by age. As reported in Table 1, we observed negative correlations between stimulated C-peptide and IDAA1C. The correlations changed over time and differed by age. At 4 years, the significant negative correlation was maintained in adult participants but was lost in young children. Importantly, using IDAA1C $\leq$9 as a surrogate of measure of residual β-cell function significantly underestimated the number of subjects with stimulated C-peptide $\geq$0.2 nmol/L, especially in children.

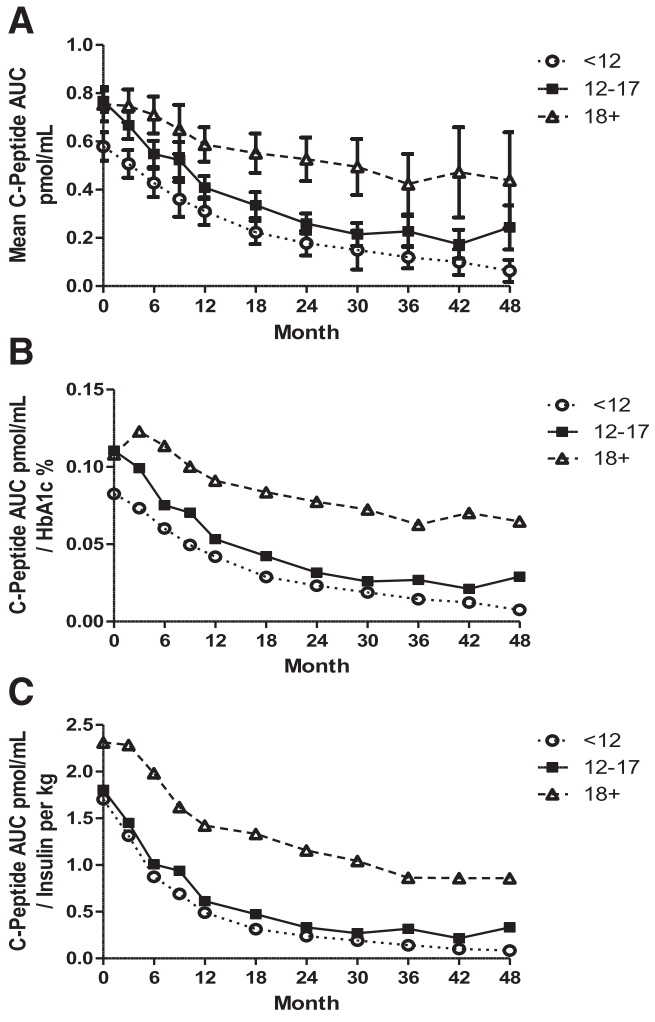

Figure 2—The mean C-peptide AUC (*A*) and the ratio between C-peptide and HbA_{1c} (*B*) or insulin use (*C*) over time by age (years). The figure was plotted with mean ± 95% CI. The mean C-peptide AUC declined over the 4 years from diagnosis and was affected by age. The inverse relationship between C-peptide and HbA_{1c} or insulin changed over time and by age.

CONCLUSIONS

We report in this study that in individuals with type 1 diabetes assessed longitudinally, neither HbA_{1c}, nor insulin use, nor a combination of both using IDAA1C, are reliable surrogates of insulin secretion compared with C-peptide responses to MMTT stimulation. Although age continues to affect the rate of fall of C-peptide up to 4 years from diagnosis, only a small percentage of subjects of any age maintain stable β-cell function at 4 years.

Understanding the natural history of residual β-cell function change after onset of type 1 diabetes is needed to test treatments designed to alter the disease process and preserve residual β-cell function. In the Diabetes Control and Complications Trial (DCCT), maintaining β-cell insulin secretion, as assessed by residual C-peptide production, demonstrated benefits for clinical diabetes management and also delayed and/or prevented complications of the disease (12–14). Evidence from islet transplantation studies demonstrated that attainment of endogenous C-peptide after islet transplantation correlates with glycemic control, including restoring hypoglycemia awareness, preventing recurrent severe hypoglycemia, and decreasing glycemic variability (15–17).

This report extends our previous analysis describing changes in MMTT-stimulated C-peptide in subjects who enrolled in Type 1 Diabetes TrialNet studies within 3 months of diagnosis by describing changes up to 4 years after diagnosis. Our previous report (18) included data from only three intervention trials (6,7,9), whereas our current analysis includes data from five intervention trials (6–10) with double the number of

Table 1—Regression models of analysis of predictors for stimulated C-peptide or HbA_{1c} over time and correlation between peak C-peptide and IDAA1C over time by age

	Estimates from regression models with stimulated peak C-peptide						
	Age (*P* value)	Sex (*P* value)	HbA_{1c} (*P* value)	Insulin (*P* value)	BMI Z (*P* value)	Baseline C-peptide (*P* value)	R^2
Log(stimulated C-peptide)							
6 months (*n* = 372)	0.005 (0.19)	−0.07 (0.23)	−0.18 (<0.0001)	−0.81 (<0.0001)	0.009 (0.77)	0.90 (<0.0001)	0.58
12 months (*n* = 370)	0.01 (0.06)	−0.13 (0.14)	−0.19 (<0.0001)	−0.90 (<0.0001)	0.004 (0.92)	1.22 (<0.0001)	0.52
24 months (*n* = 299)	0.03 (0.003)	−0.08 (0.54)	−0.18 (0.0002)	−0.97 (<0.0001)	−0.01 (0.88)	1.58 (<0.0001)	0.46
36 months (*n* = 73)	0.02 (0.30)	0.01 (0.96)	−0.23 (0.03)	−1.04 (0.06)	−0.09 (0.60)	1.76 (<0.0001)	0.44
48 months (*n* = 43)	0.01 (0.62)	0.02 (0.97)	−0.27 (0.03)	−0.69 (0.36)	−0.09 (0.59)	2.70 (<0.0001)	0.52
	Estimates from regression models with HbA_{1c}						
	Age (*P* value)	Sex (*P* value)	Log(stimulated C-peptide) (*P* value)	Insulin (*P* value)	BMI Z (*P* value)	Baseline HbA_{1c} (*P* value)	R^2
HbA_{1c}							
6 months (*n* = 354)	−0.02 (0.004)	−0.06 (0.58)	−0.55 (<0.0001)	0.56 (0.02)	0.08 (0.15)	0.16 (0.001)	0.33
12 months (*n* = 354)	−0.02 (0.002)	−0.09 (0.49)	−0.28 (<0.0001)	0.76 (0.001)	0.08 (0.21)	0.19 (0.0007)	0.28
24 months (*n* = 285)	−0.03 (0.02)	−0.05 (0.80)	−0.16 (0.02)	0.66 (0.02)	0.009 (0.92)	0.15 (0.04)	0.16
36 months (*n* = 73)	−0.03 (0.21)	−0.42 (0.23)	−0.12 (0.32)	1.42 (0.02)	0.16 (0.37)	0.29 (0.12)	0.30
48 months (*n* = 43)	−0.06 (0.15)	0.05 (0.93)	−0.09 (0.67)	1.02 (0.35)	−0.04 (0.86)	0.21 (0.46)	0.19

	Correlation between peak C-peptide and IDAA1C over time by age		
Duration of diabetes (years)	Peak C-peptide ≥0.2 nmol/L % (95% CI)	IDAA1C* ≤9 % (95% CI)	Correlation coefficient (*P* value)
At 1 year			
<12	71.2 (62.1, 78.5)	29.0 (21.1, 37.3)	−0.55 (<0.0001)
12–17	85.7 (79.4, 90.2)	29.7 (23.0, 36.7)	−0.69 (<0.0001)
≥18	94.7 (88.5, 97.6)	63.7 (53.9, 71.9)	−0.68 (<0.0001)
At 2 years			
<12	42.8 (33.4, 51.8)	9.8 (5.2, 16.0)	−0.24 (0.03)
12–17	65.3 (57.4, 72.1)	13.2 (8.6, 18.8)	−0.45 (<0.0001)
≥18	80.5 (71.6, 86.8)	52.9 (43.0, 61.8)	−0.65 (<0.0001)
At 3 years			
<12	26.9 (17.6, 37.1)	—	−0.41 (0.05)
12–17	36.4 (27.9, 45.0)	6.3 (3.0, 11.2)	−0.48 (0.003)
≥18	64.0 (52.6, 73.4)	39.1 (28.8, 49.2)	−0.72 (<0.0001)
At 4 years			
<12	9.6 (3.1, 20.5)	—	−0.06(0.85)
12–17	27.0 (18.5, 36.1)	2.7 (0.8, 6.8)	−0.34(0.18)
≥18	61.2 (48.9, 71.4)	20.4 (9.2, 34.8)	−0.70 (0.003)

*IDAA1C = HbA_{1c} (percentage) + 4 × (insulin dose [in units/kg/day]).

participants. We demonstrated more rapid C-peptide decline during the first year compared with the subsequent 2 to 4 years, and only a few subjects of any age maintained β-cell function at 4 years. We extend our previous report by confirming the effect of age on residual β-cell function out to 4 years from diagnosis. Although limited to those enrolled in TrialNet clinical trials, our findings of residual β-cell function changes over time and the age effect on insulin secretion at diagnosis are comparable with a recent cross-sectional cohort study report of the prevalence of detectable C-peptide in those with long-standing disease (19).

Individuals living with other autoimmune diseases, such as rheumatoid arthritis, have seen a recent transformation in care from symptomatic treatment to disease-modifying treatment (20). This is the same goal we wish to achieve in type 1 diabetes, transitioning from treating hyperglycemia to treating with agents that alter the disease course. These efforts involve clinical trials before the onset of clinical disease (prevention studies) and also trials soon after diagnosis (intervention trials) aimed to preserve β-cell function. The first trials using immune therapies to alter the disease course considered the aim of prolonging the honeymoon period after diagnosis, defined as taking individuals off of insulin. Indeed, an early trial of cyclosporine (21) reported 24.1% of treated subjects were off insulin (in complete remission) vs. 5.8% of the placebo group at 9 months. Some studies have still reported this end point. Subsequent studies looked toward a direct measure of the biological aim of these interventions and used C-peptide, usually in response to MMTT stimulation, as the primary end point of trials (5,7–10,22–26). Corollary clinical end points of glycemic control and insulin dose have been also be used, including combination end points of both of these variables (11,22,23). Although the ultimate goal of all such trials is to identify clinically important therapies, there are theoretical

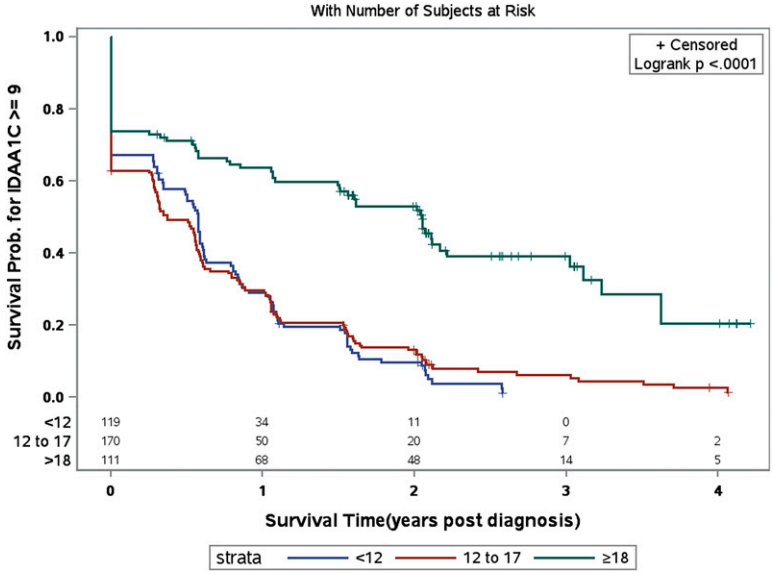

Figure 3—Probability (Prob.) of subjects with IDAA1C ≤9 over time by age (years).

and practical issues with these end points. For example, with tight glycemic control as standard of care, investigators work to achieve this goal for all trial participants, aiming to have placebo and treatment groups have equal HbA_{1c}. Other measures of glycemic control are too infrequently seen in persons with new-onset disease to serve as clinical trial end points (e.g., severe hypoglycemia or diabetic ketoacidosis) or are not collected consistently by study participants (home glucose monitoring), thus leading to potential bias. In contrast to rigid meals and limited types of insulin and dosing schedules that were the standard of care in the 1980s, there is now wide variability in insulin delivery methods and insulin types used. The units/kg of insulin use may vary considerably according to physician and patient choices, including whether one is using continuous subcutaneous insulin infusion or injections, the amount of carbohydrate consumed, and the amount of exercise. Thus, using insulin use in units/kg is unlikely to strongly correlate with residual insulin secretion in multicenter clinical trials without limiting the other known behavioral factors.

We observed only weak relationships between the biological measure of interest (stimulated insulin secretion) and the clinical measures (HbA_{1c} and/or insulin use), whether alone or in combination. Moreover, we found that time influences this relationship, making them poor outcome measures for evaluating the effect of therapy on preservation of β-cell function. We highlight the well-known effect of age not only on C-peptide over time but now also on the relationship of C-peptide to other clinical variables of HbA_{1c} and insulin dose by age.

The aim of disease-modifying therapies in type 1 diabetes is to prevent the clinical presence of disease altogether. An interim goal would be a markedly less intensive needs for insulin administration and glucose monitoring without hypoglycemia or risk of long-term complications. A necessary step to these end points in those after clinical diagnosis is to first demonstrate that a new therapy can robustly and safely preserve β-cell function. Most clinical trials of disease-modifying therapies to date have used 1 and 2 years as the primary end point to determine the effects of therapy. In addition to reemphasizing that clinical trials aiming to preserve β-cell function should use measures of insulin secretion as the outcome measure, the data presented here suggest that continued follow-up of such individuals could provide additional evidence of the effect of therapy because few individuals, particularly children, have significant insulin secretion after 4 years, and <5% of all individuals of any age maintain their baseline C-peptide levels at that time point.

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References

1. Skyler JS, Greenbaum CJ, Lachin JM, et al.; Type 1 Diabetes TrialNet Study Group. Type 1 Diabetes TrialNet–an international collaborative clinical trials network. Ann N Y Acad Sci 2008; 1150:14–24
2. Greenbaum CJ, Mandrup-Poulsen T, McGee PF, et al.; Type 1 Diabetes Trial Net Research Group; European C-Peptide Trial Study Group. Mixed-meal tolerance test versus glucagon stimulation test for the assessment of beta-cell function in therapeutic trials in type 1 diabetes. Diabetes Care 2008;31:1966–1971
3. Palmer JP, Fleming GA, Greenbaum CJ, et al. C-peptide is the appropriate outcome measure for type 1 diabetes clinical trials to preserve beta-cell function: report of an ADA workshop, 21-22 October 2001. Diabetes 2004;53:250–264
4. Mortensen HB, Hougaard P, Swift P, et al.; Hvidoere Study Group on Childhood Diabetes. New definition for the partial remission period in children and adolescents with type 1 diabetes. Diabetes Care 2009;32:1384–1390
5. Sherry N, Hagopian W, Ludvigsson J, et al.; Protégé Trial Investigators. Teplizumab for treatment of type 1 diabetes (Protégé study): 1-year results from a randomised, placebo-controlled trial. Lancet 2011;378:487–497
6. Moran A, Bundy B, Becker DJ, et al.; Type 1 Diabetes TrialNet Canakinumab Study Group; AIDA Study Group. Interleukin-1 antagonism in type 1 diabetes of recent onset: two multicentre, randomised, double-blind, placebo-controlled trials. Lancet 2013;381:1905–1915
7. Wherrett DK, Bundy B, Becker DJ, et al.; Type 1 Diabetes TrialNet GAD Study Group. Antigen-based therapy with glutamic acid decarboxylase (GAD) vaccine in patients with recent-onset type 1 diabetes: a randomised double-blind trial. Lancet 2011;378:319–327

8. 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 randomised, double-blind, placebo-controlled trial. Lancet 2011;378:412–419
9. Gottlieb PA, Quinlan S, Krause-Steinrauf H, et al.; Type 1 Diabetes TrialNet MMF/DZB Study Group. Failure to preserve beta-cell function with mycophenolate mofetil and daclizumab combined therapy in patients with new-onset type 1 diabetes. Diabetes Care 2010;33:826–832
10. 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
11. Herold KC, Gitelman SE, Masharani U, et al. A single course of anti-CD3 monoclonal antibody hOKT3gamma1(Ala-Ala) results in improvement in C-peptide responses and clinical parameters for at least 2 years after onset of type 1 diabetes. Diabetes 2005;54:1763–1769
12. 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
13. Lachin JM, McGee P, Palmer JP; DCCT/EDIC Research Group. Impact of C-peptide preservation on metabolic and clinical outcomes in the Diabetes Control and Complications Trial. Diabetes 2014;63:739–748
14. The Diabetes Control and Complications Trial Research Group. Effect of intensive 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
15. Brooks AM, Oram R, Home P, Steen N, Shaw JA. Demonstration of an intrinsic relationship between endogenous C-peptide concentration and determinants of glycemic control in type 1 diabetes following islet transplantation. Diabetes Care 2015;38:105–112
16. Vantyghem MC, Raverdy V, Balavoine AS, et al. Continuous glucose monitoring after islet transplantation in type 1 diabetes: an excellent graft function (β-score greater than 7) is required to abrogate hyperglycemia, whereas a minimal function is necessary to suppress severe hypoglycemia (β-score greater than 3). J Clin Endocrinol Metab 2012;97:E2078–E2083
17. Kessler L, Passemard R, Oberholzer J, et al.; GRAGIL Group. Reduction of blood glucose variability in type 1 diabetic patients treated by pancreatic islet transplantation: interest of continuous glucose monitoring. Diabetes Care 2002;25:2256–2262
18. Greenbaum CJ, Beam CA, Boulware D, et al.; Type 1 Diabetes TrialNet Study Group. Fall in C-peptide during first 2 years from diagnosis: evidence of at least two distinct phases from composite Type 1 Diabetes TrialNet data. Diabetes 2012;61:2066–2073
19. Davis AK, DuBose SN, Haller MJ, et al.; T1D Exchange Clinic Network. Prevalence of detectable C-peptide according to age at diagnosis and duration of type 1 diabetes. Diabetes Care 2015;38:476–481
20. Zampeli E, Vlachoyiannopoulos PG, Tzioufas AG. Treatment of rheumatoid arthritis: unraveling the conundrum. J Autoimmun 2015;65:1–18
21. Feutren G, Papoz L, Assan R, et al. Cyclosporin increases the rate and length of remissions in insulin-dependent diabetes of recent onset. Results of a multicentre double-blind trial. Lancet 1986;2:119–124
22. Rigby MR, Harris KM, Pinckney A, et al. Alefacept provides sustained clinical and immunological effects in new-onset type 1 diabetes patients. J Clin Invest 2015;125:3285–3296
23. Rigby MR, DiMeglio LA, Rendell MS, et al.; T1DAL Study Team. Targeting of memory T cells with alefacept in new-onset type 1 diabetes (T1DAL study): 12 month results of a randomised, double-blind, placebo-controlled phase 2 trial. Lancet Diabetes Endocrinol 2013;1:284–294
24. Herold KC, Gitelman SE, Ehlers MR, et al.; AbATE Study Team. Teplizumab (anti-CD3 mAb) treatment preserves C-peptide responses in patients with new-onset type 1 diabetes in a randomized controlled trial: metabolic and immunologic features at baseline identify a subgroup of responders. Diabetes 2013;62:3766–3774
25. Pescovitz MD, Greenbaum CJ, Bundy B, et al.; Type 1 Diabetes TrialNet Anti-CD20 Study Group. B-lymphocyte depletion with rituximab and β-cell function: two-year results. Diabetes Care 2014;37:453–459
26. Orban T, Bundy B, Becker DJ, et al.; Type 1 Diabetes TrialNet Abatacept Study Group. Costimulation modulation with abatacept in patients with recent-onset type 1 diabetes: follow-up 1 year after cessation of treatment. Diabetes Care 2014;37:1069–1075