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Changes in Beta Cell Function during the Proximate Post-Diagnosis Period in Persons with Type 1 Diabetes

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Abstract

Objective—Prior studies examining beta-cell preservation in type 1 diabetes have predominantly assessed stimulated C-peptide concentrations ~10 weeks after diagnosis. We examined whether earlier assessments might aid in prediction of beta cell function over time.

Methods—Using data from a multi-center randomized trial assessing the effect of intensive diabetes management initiated within one week of diagnosis, we assessed which clinical factors predicted 90-min mixed-meal tolerance test (MMTT) stimulated C-peptide values obtained 2 and 6 weeks after diagnosis. We also studied associations of these factors with C-peptide values at 1 and 2 years post-diagnosis. Data from intervention and control groups were pooled.

Results—Among 67 study participants (mean age 13.3±5.7 years, range 7.8-45.7 years) in multivariable analyses, C-peptide increased from baseline to 2 weeks and then 6 weeks. C-peptide levels at these times were significantly correlated with 1- and 2-year C-peptide concentrations (all $p<0.001$), with the strongest observed associations between 6-week C-peptide and the one- and two-year values ($r=0.66$ and $r=0.61$ respectively). In multivariable analyses, greater baseline and

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6-week C-peptide, and older age independently predicted greater 1 and 2-year C-peptide concentrations.

Conclusions—C-peptide assessments close to diagnosis were predictive of subsequent C-peptide production. Our data demonstrate a clear increase in C-peptide over the initial 6 weeks after diabetes diagnosis followed by a plateau. Our data do not suggest that MMTT assessments performed closer to diagnosis than 6 weeks would improve prediction of subsequent residual beta cell function.

Trial Registry Number: NCT00760526

Keywords

clinical science; insulin secretions in vivo; diabetes in childhood

Introduction

At the time of the clinical diagnosis of type 1 diabetes, most individuals have residual functioning pancreatic beta cells that continue to produce some insulin for several additional years. Over time, these beta cells gradually lose function and decrease in number. However, even limited beta cell function is of clinical import as residual C-peptide secretion is related to lower incidences of hypoglycemia, hyperglycemia, and diabetic ketoacidosis (1, 2). Therefore, in persons with new onset type 1 diabetes as well as in those at high risk of type 1 diabetes, a variety of intervention studies have been performed, including intensive metabolic control and immunomodulatory therapy trials in attempts to preserve this endogenous insulin secretion (3-8). To date, such studies have had only limited success. Given that many immunomodulatory therapies appear to have their greatest effect in those earliest in the progressive course of type 1diabetes, there could be great utility to identifying participants with the greatest residual beta cell function immediately at diagnosis.

Beta cell insulin production is commonly assessed serially using responses to a known secretagogue. The most commonly-used and validated assessment is the stimulated C-peptide response to a mixed meal tolerance test (MMTT) (9). Islet-cell preservation studies have assessed residual beta cell function in new-onset participants based upon peak MMTT-stimulated C-peptide concentrations measured 6 to 12 weeks after diagnosis (5, 7, 8). Yet, assessments of beta cell function more proximate to diagnosis could be useful in order to permit earlier recruitment of patients into intervention studies at a time when beta cells are recovering from exposure to a chronically hyperglycemic environment and new beta cells are being recruited from other pancreatic cell pools. Earlier assessments of insulin production also provide additional insights into the trajectory first of increases and then decreases in beta cell insulin production over time after diagnosis.

As part of a DirecNet-TrialNet randomized trial to assess the effect of intensive insulin management from the time of diagnosis of type 1 diabetes on preservation of residual insulin secretion, serial C-peptide data were obtained using MMTT performed at regular intervals starting within one week of diagnosis of type 1 diabetes. We examined the utility of stimulated C-peptide measurements and other clinical factors assessed within 2 weeks of

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type 1 diabetes diagnosis in predicting subsequent beta cell function in order to determine whether such screening might be as predictive or more predictive than 6 week C-peptide assessments and which individuals at the time of diagnosis have the greatest ultimate C-peptide concentrations at 1 and 2 years.

Methods

Data were obtained during the TrialNet-DirecNet randomized trial of the effect of metabolic control at the onset of diabetes on the progression of type 1 diabetes. The trial evaluated the effectiveness of intensive insulin management initiated within 7 days of diagnosis, using a three-day course of inpatient hybrid closed-loop control followed by outpatient sensor-augmented pump therapy compared with a control usual care group receiving standard diabetes management. Participants were randomly assigned to an intensive care group or a usual care group in a 2:1 ratio, stratified by presence of diabetic ketoacidosis (DKA) at the time of diagnosis as defined by the DCCT criteria (10). Data from intervention and control groups were pooled since the study intervention was not found to have any influence on C-peptide measurements (3) or other clinical outcomes assessed during the primary trial at any time point. Details of the protocol have been published elsewhere (3). Full protocol details are available at http://direcnet.jaeb.org/Studies.aspx and on www.clinicaltrials,gov (NCT00760526). The study protocol was approved by the institutional review boards of all 5 participating clinical centers. Written informed consent was obtained from adult participants and parents/guardians of minor participants. Children under 18 provided written assent as required by local regulations.

In brief, two-hour MMTTs were conducted using the standard Type 1 Diabetes TrialNet protocol (9, 11) at 2, 6 and 13 weeks after diagnosis, and then every 3 months thereafter through 2 years. At study baseline (within 1 week after diagnosis) a modified MMTT was performed, with C-peptide measured at 0 and 90 min, C-peptide, HbA_{1c} concentrations and islet autoantibodies were measured for each participant at the core TrialNet laboratories (Northwest Lipid Research Laboratory [HbA1c] and the Universities of Colorado and Florida [islet autoantibodies]). C-peptide was performed by two site immuno-enzymometeric assay (TOSOH, Biosciences, Inc., South San Francisco, CA), with inter-assay co-efficients of variation for Low, Medium and High C peptide controls of 3.2%, 1.6% and 1.8%, respectively. Only autoantibody positive subjects were included in the analyses: 62 participants demonstrated pancreatic autoantibodies at the time of diagnosis (17 had a single autoantibody, 45 multiple). Five more participants demonstrated a pancreatic autoantibody (other than insulin) later during the first 12 months (four had none at diagnosis but then developed autoantibodies before the 12 month visit, and one did not have autoantibodies tested at the time of diagnosis but had positive autoantibodies at the time of the 12 month visit).

Statistical Methods

Data from the intensive care and usual care groups were combined for analyses. Log-transformed C-peptide values at baseline and 90 minutes during MMTTs were used in the analyses, as this has been shown to be a sensitive and specific measure of peak insulin

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secretion (12). The proportion of subjects with C-peptide levels > 0.2 pmol/ml was also examined, as this a threshold that is associated with better clinical outcomes (2).

Both univariable and multivariable generalized least square regression models were used to assess associations between factors at diagnosis with changes in C-peptide concentrations during the early post-diagnosis period (baseline to 2 weeks and baseline to 6 weeks). For multivariable models, a forward stepwise selection method was used; factors with p-value < 0.10 remained in the model, but only factors with a p-value of < 0.01 were considered statistically significant (due to the multiple factors evaluated). Similar models also were constructed to evaluate the association of factors at diagnosis and C-peptide concentrations from the early post-diagnosis period with C-peptide values at 1 and 2 years.

Results

Sixty-seven participants (age 7.8 to 45.7 years, mean 13.3 ± 5.7 years) were enrolled within 6 days of type 1 diabetes diagnosis (mean 2.9±1.7 days). Twenty participants (30%) were in DKA at diagnosis. Mean HbA_{1c} was 11.6 ± 2.5% (103 ± 27 mmol/mol) at diagnosis, 7.3 ± 1.2% (56 ± 13 mmol/mol) at 1 year and 7.6 ± 1.2% (60 ± 13 mmol/mol) at 2 years. Sixty-five of the 67 subjects completed a MMTT at enrollment; 62 had a 2 week MMTT and 64 a 6 week MMTT assessment. All 67 participants completed the 12-month visit and 65 completed the 24 month visit.

At the time of the initial assessment shortly after diagnosis, 75% of participants had a 90-minute stimulated C-peptide concentration of > 0.2 pmol/ml (Figure 1). By 6 weeks that level was achieved by 100%, and then came down by 24 months to 56%.

Predictors of C-peptide Concentrations After 2 and 6 Weeks

C-peptide concentrations increased from baseline to 2 weeks and then 6 weeks. In univariable analyses, greater increases in C-peptide from baseline to 2 weeks and baseline to 6 weeks were seen in participants with higher HbA_{1c} at diagnosis (p=0.02 and <0.001, respectively), DKA at diagnosis (p=0.01 at both time points) and lower baseline C-peptide concentrations (p<0.001 at both time points). However, in multivariable analyses, only lower baseline C-peptide levels remained significant (P<0.001 at both time points, Table 1). Participant age at diagnosis and number of islet autoantibodies were not associated with change in C-peptide concentrations from baseline to 2 weeks or baseline to 6 weeks (Table 1).

Predictors of C-peptide Concentrations at 1 Year and 2 Years

Participants who were older at the time of diagnosis, had higher C-peptide levels at 1 and 2 years. Baseline, 2 week and 6 week C-peptide concentrations were all associated with 1 year and 2 year C-peptide concentrations (Spearman r ranging from 0.51 to 0.66, all p<0.001, Table 2), with the strongest observed correlation between 6-week C-peptide and 1-year C-peptide concentrations. However, the changes in C-peptide concentration from baseline to 2 weeks and from baseline to 6 weeks were not significantly related to 1 year or 2 year C-peptide concentrations (Table 2).

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In univariable regression models, older age at diagnosis, lower HbA_{1c} at diagnosis, and higher baseline, 2 week, and 6-week C-peptide concentrations were all associated with higher 1-year and 2-year C-peptide concentrations. In multivariable analyses, all but HbA_{1c} remained significant (Table 3). We also examined whether early peak C-peptide responses were able to predict which participants ultimately had C-peptide levels above the threshold of 0.2 pmol/mL, and in multivariable models only the 6-week C-peptide level was significant. The presence of DKA at diagnosis and number of islet autoantibodies were not associated with the 1-year or 2-year C-peptide concentrations.

Discussion

Although C-peptide measures obtained within one week and then at two weeks after diagnosis were significantly correlated to those observed later, the values obtained from these very early MMTT assessments were not as strongly associated with subsequent residual stimulated beta cell insulin secretion as later measures. This is likely due to a combination of factors. One is that our cohort contained a number of persons with a relatively severe onset of type 1 diabetes (e.g. higher HbA_{1c}s at diagnosis, DKA at diagnosis). These persons had lower initial stimulated C-peptide levels and were more likely to see greater increases in C-peptide from the time of diagnosis out to 6 weeks. This could be expected as those persons likely had more acute suppression of any remaining islet cell function due to acidosis or glucose toxicity, which recovered as those insults were mitigated. Additionally, the greater correlation of 6-week C-peptide concentrations to 1 and 2 year values compared to earlier-assessed time points might also reflect short-term regeneration of beta-cell mass (13). As expected from previous studies, in our cohort of individuals with a mean age of 13.3 years, we also observed that those individuals who were older had greater residual C-peptide levels at 1 and 2 years (14, 15).

Prior studies of random and MMTT-stimulated C-peptide concentrations in cohorts of individuals with very recently diagnosed type 1 diabetes are limited. Most have been cross-sectional rather than longitudinal and/or enrolled very limited numbers of recently-diagnosed persons (9). In 1978, Ludvigsson and Heding looked at fasting c-peptides over up to 9 months in 12 children with new onset T1D managed on insulin once or twice daily (16). Although a few had increases in c-peptide by 1 month post diagnosis, generally the c-peptide concentrations were the same as at diagnosis, and then showed a subsequent steady decline. In 1982, Madsbad and colleagues examined 15 adult subjects randomized to either conventional treatment (with 1-2 injections per day of long-acting insulin (lente or Monotard®) with or without regular (Actrapid®) insulin) or regular insulin given nine times per day (17). They performed MMTT on the day of admission and then one week, two weeks, 90 days, and 180 days later. Their data demonstrated a significant difference in secreted c-peptide area under the curve at 2 weeks that was not maintained. As in our population, c-peptide rose after diagnosis before declining by 6 months after diagnosis.

Nearly 20 years ago, Linn and colleagues described post-diagnosis insulin reserve and sensitivity in a cohort of 24 adult subjects with new-onset type 1 diabetes managed after diagnosis with intermediate acting insulin, with regular insulin as needed for post-prandial glucoses greater than 198 mg/dl (11 mmol/L) (18). Their data show changes in insulin

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sensitivity (derived from euglycemic-hyperinsulinemic clamp) over the time after diagnosis which also demonstrate initial increases followed by a slow decline, similar to the trajectory we observed in longitudinal C-peptide assessments. Although they observed a gradual increase in glucagon-stimulated C-peptide after diagnosis, this phase continued out to 6 months followed by a plateau. Mortensen and colleagues looked at predictors of residual stimulated C-peptide concentrations at 1, 6, and 12 months after diagnosis in 275 children with a mean age of 9.1 years at diagnosis and modeled predictors of this change (19). They found gradual declines in C-peptide over time, but did not have early enough assessments to document the beta cell recovery phase after diagnosis. Our data, therefore, add a new phase to the previously-described trajectories in C-peptide changes in a predominantly pediatric population as assessed by MMTT (20), with a clear increase in C-peptide associated with the type 1 diabetes “honeymoon” remission period followed by a 6 week to 3 month plateau, and then gradual decline out to 2 years

The results of this study may not be entirely generalizable to other cohorts of persons with new-onset type 1 diabetes. Our study cohort was comprised predominantly of children. Our study participants also achieved excellent glycemic control during the first two years reflected by their low HbA_{1c} levels and had extremely high and rapid adoption of pump use (by 1 year, 91% were using insulin pumps, which increased to 94% at 2 years). It is possible that the factors which influence C-peptide trajectories would be different at greater extremes of glycemic control.

In summary, C-peptide assessments performed within the first 6 weeks of diagnosis of T1D, as expected, were predictive of subsequent C-peptide production. Since all participants who had stimulated C-peptide levels above a > 0.2 pmol/ml threshold at baseline and/or 2 weeks continued to exceed this value at the 6 week visit, it is acceptable to continue to offer MMTT screening of potential participants in clinical trials of interventions designed to improve or maintain endogenous insulin production at times very proximate to diagnosis. However, the stronger correlation of stimulated C-peptide measures obtained 6 weeks after diagnosis to 1 and 2 year values suggests that it is also satisfactory to continue to perform MMTT assessments nearer to 6 weeks after diagnosis when determining eligibility for entry into trials designed to preserve beta cell mass.

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Appendix

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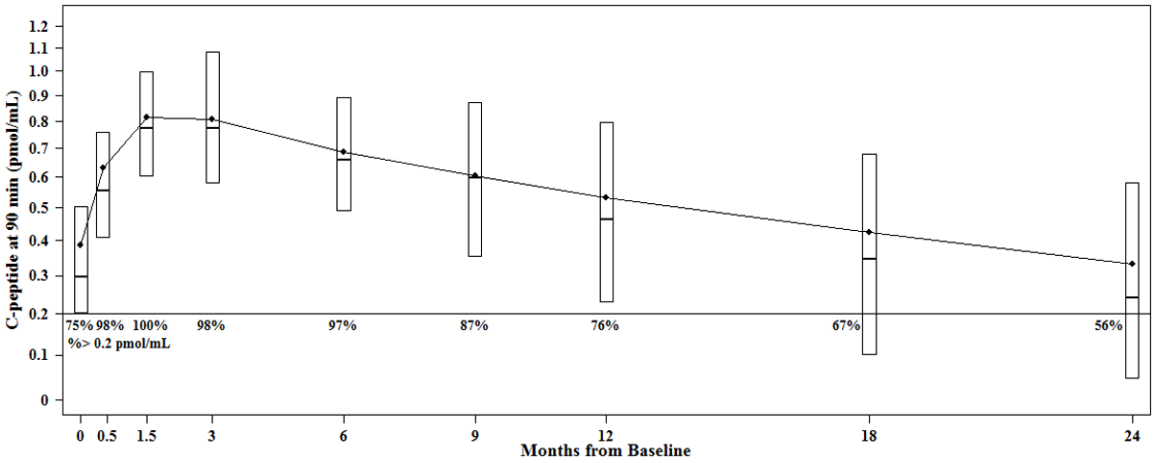

Figure 1. 90-min C-peptide at each visit*

Box plots for 90-min stimulated C-peptide at each follow-up visit. The bottom and top of each box denote the 25th and 75th percentiles, respectively, the line inside the box denotes the median, and the dot is the geometric mean.

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Table 1

Regression models using factors at diagnosis to predict change in C-peptide from baseline to 2 week/6 week

	Log(C-peptide+1) Change (2 week – Baseline)				Log(C-peptide+1) Change (6 week – Baseline)			
	N	**Mean (99% C.I.)**	**Univariable p-value**	**Multivariable p-value**	**N**	**Mean (99% C.I.)**	**Univariable p-value**	**Multivariable p-value**
Age at baseline (years)			0.88[a]	0.07[a]			0.30[a]	N/A[b]
7-<12 years	26	+0.15 (+0.07, +0.22)			28	+0.26 (+0.18, +0.33)		
≥12 years	35	+0.16 (+0.09, +0.24)			35	+0.28 (+0.18, +0.38)		
HbA1c at diagnosis (%)			0.02[a]	N/A[b]			<0.001[a]	0.06[a]
<10.0% (<86 mmol/mol)	19	+0.07 (-0.03, +0.17)			18	+0.12 (-0.01, +0.24)		
≥10.0% (≥86mmol/mol)	42	+0.20 (+0.14, +0.25)			45	+0.33 (+0.27, +0.39)		
DKA at diagnosis								
Yes	16	+0.24 (+0.11, +0.37)	0.01	0.08	18	+0.36 (+0.26, +0.46)	0.01	N/A[b]
No	45	+0.13 (+0.07, +0.18)			45	+0.23 (+0.16, +0.31)		
Positive Autoantibodies at diagnosis								
Multiple	42	+0.17 (+0.10, +0.23)	0.30	N/A[b]	45	+0.28 (+0.20, +0.36)	0.54	N/A[b]
None/one	19	+0.13 (+0.03, +0.22)			18	+0.25 (+0.15, +0.35)		
Baseline log(C-peptide +1)			<0.001[a]	<0.001[a]			<0.001[a]	<0.001[a]
<0.25	28	+0.22 (+0.14, +0.30)			31	+0.34 (+0.27, +0.42)		
≥0.25	33	+0.10 (+0.04, +0.17)			32	+0.20 (+0.10, +0.30)		

[a] p-value calculated based on continuous variable

[b] Multivariable p-value not available because the variable was not retained in the final model after stepwise selection procedures

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Table 2

Spearman correlations between early predictors and C-peptide at 1 year and 2 year

	1-yr C-peptide	2-yr C-peptide
Age at baseline		
Correlation	0.46	0.46
p-value	<0.001	<0.001
N	67	64
HbA_{1c}		
Correlation	-0.04	-0.03
p-value	0.75	0.80
N	67	64
Baseline C-peptide		
Correlation	+0.53	+0.51
p-value	<0.001	<0.001
N	65	62
2 week C-peptide		
Correlation	+0.59	+0.58
p-value	<0.001	<0.001
N	62	60
6 week C-peptide		
Correlation	+0.66	+0.61
p-value	<0.001	<0.001
N	64	62
C-peptide Change (2wk – baseline)		
Correlation	-0.02	+0.01
p-value	0.88	0.96
N	61	59
C-peptide Change (6wk – baseline)		
Correlation	+0.07	+0.07
p-value	0.58	0.61
N	63	61

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Table 3

Regression models for predicting 90 minute C-peptide at 1 year and 2 years

	Log(C-peptide+1) at 1 year				Log(C-peptide+1) at 2 year			
	N	**Mean (99% C.I.)**	**Univariable p-value**	**Multivariable p-value**	**N**	**Mean (99% C.I.)**	**Univariable p-value**	**Multivariable p-value**
Age at baseline (years)			<0.001[a]	<0.001[a]			<0.001[a]	<0.001[a]
7-<12 years	30	0.31 (0.21, 0.42)			28	0.18 (0.08, 0.27)		
≥12 years	37	0.52 (0.38, 0.65)			36	0.37 (0.23, 0.51)		
HbA1c at diagnosis (%)			0.002[a,b]	0.07[a]			0.004[a,b]	N/A[c]
<10.0% (<86 mmol/mol)	19	0.53 (0.31, 0.75)			19	0.38 (0.16, 0.61)		
≥10.0% (≥86 mmol/mol)	48	0.38 (0.29, 0.48)			45	0.24 (0.15, 0.34)		
DKA								
Yes	20	0.38 (0.22, 0.54)	0.41	N/A[c]	18	0.23 (0.09, 0.38)	0.34	N/A[c]
No	47	0.45 (0.33, 0.56)			46	0.31 (0.19, 0.42)		
Positive Autoantibodies[a]								
Multiple	45	0.39 (0.30, 0.49)	0.12	N/A[c]	43	0.26 (0.16, 0.35)	0.14	N/A[c]
None/one	21	0.51 (0.30, 0.73)			20	0.37 (0.16, 0.57)		
Baseline log(C-peptide +1)			<0.001[a]	0.005[a]			<0.001[a]	0.01[a]
<0.25	31	0.30 (0.21, 0.40)			29	0.17 (0.08, 0.26)		
≥0.25	34	0.54 (0.40, 0.68)			33	0.39 (0.24, 0.53)		
Log(C-peptide+1) at 2 week			<0.001[a]	N/A[c]			<0.001[a]	N/A[c]
<0.45	32	0.28 (0.20, 0.36)			31	0.15 (0.08, 0.23)		
≥0.45	30	0.61 (0.47, 0.76)			29	0.45 (0.31, 0.60)		
Log(C-peptide+1) at 6 week			<0.001[a]	<0.001[a]			<0.001[a]	0.002[a]
<0.55	30	0.28 (0.20, 0.37)			29	0.16 (0.07, 0.25)		
≥0.55	34	0.57 (0.44, 0.71)			33	0.41 (0.27, 0.55)		

[a] p-value calculated based on continuous variable

[b] Polynomial term included in the model

[c] Multivariable p-value not available because the variable was not retained in the final model after stepwise selection