Prevalence of Detectable C-Peptide According to Age at Diagnosis and Duration of Type 1 Diabetes

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OBJECTIVE

It is generally accepted that complete β-cell destruction eventually occurs in individuals with type 1 diabetes, which has implications for treatment approaches and insurance coverage. The frequency of residual insulin secretion in a large cohort of individuals at varying ages of diagnosis and type 1 diabetes duration is unknown.

RESEARCH DESIGN AND METHODS

The frequency of residual insulin secretion was determined by measurement of nonfasting serum C-peptide concentration in 919 individuals with type 1 diabetes according to prespecified groups based on age at diagnosis and duration of disease (from 3 to 81 years' duration). Stimulated C-peptide was measured in those with detectable nonfasting values and a group of those with undetectable values as control.

RESULTS

The overall frequency of detectable nonfasting C-peptide was 29%, decreasing with time from diagnosis regardless of age at diagnosis. In all duration groups, the frequency of C-peptide was higher with diagnosis age >18 years compared with ≤18 years. Nineteen percent of those with undetectable nonfasting C-peptide were C-peptide positive upon stimulation testing.

CONCLUSIONS

The American Diabetes Association's definition of type 1 diabetes as "usually leading to absolute insulin deficiency" results in clinicians often considering the presence of residual insulin secretion as unexpected in this population. However, our data suggest that residual secretion is present in almost one out of three individuals 3 or more years from type 1 diabetes diagnosis. The frequency of residual C-peptide decreases with time from diagnosis regardless of age at diagnosis, yet at all durations of disease, diagnosis during adulthood is associated with greater frequency and higher values of C-peptide.

Type 1 diabetes results from an immune-mediated destruction of pancreatic β-cells that begins long before, and is believed to continue long after, the clinical diagnosis of type 1 diabetes (1). Measurement of C-peptide is a well-accepted method for the quantification of endogenous insulin secretion and β-cell function. While fasting and random measures of C-peptide can be used, the mixed-meal tolerance test (MMTT) to measure stimulated C-peptide has been validated and is used as the primary end point measure in clinical trials seeking to assess insulin secretion in type 1 diabetes (2–4). The Diabetes Control and Complications Trial (DCCT) reported that a stimulated C-peptide

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value >0.2 nmol/L was associated with less hypoglycemia, retinopathy, and nephropathy (5). A more recent DCCT report indicates that even lower levels of C-peptide are associated with fewer diabetes complications (6). Similarly, even individuals with type 1 diabetes who had only a partial response to islet cell transplantation (i.e., were not insulin independent or able to normalize glycemic control) were found to have a marked reduction in hypoglycemic events (7).

The natural history of β-cell function and the presence of residual C-peptide during the first few years after diagnosis have been extensively studied; most individuals have some residual insulin secretion at the time of diagnosis and within 1–2 years after diagnosis (8,9). At the opposite end of the spectrum, one study reported that 67% of 411 individuals with type 1 diabetes of at least 50 years' duration had detectable random C-peptide levels (10). This study included a highly selective cohort of survivors from an era prior to present management paradigms and thus may not be characteristic of a general, current type 1 diabetes population. Others have also reported on the presence of residual insulin secretion in type 1 diabetes; these studies tested selected cohorts (11–13), small numbers of participants (14), or individuals with a limited duration of disease (15). In addition to the presence of diabetes-related autoantibodies, history of other autoimmune diseases, and family history of type 1 diabetes, the absence or presence of endogenous insulin secretion is often used to classify patients as having type 1 diabetes versus type 2 diabetes. Therefore, understanding the frequency of residual secretion in a large cohort has important clinical implications.

In this study, we aimed to determine the frequency of detectable nonfasting C-peptide (≥0.017 nmol/L) and levels ≥0.2 nmol/L in a large cohort of individuals with type 1 diabetes, according to age at diagnosis and type 1 diabetes duration. Results of nonfasting C-peptide measurements also were evaluated in comparison with MMTT results.

RESEARCH DESIGN AND METHODS

The study was conducted at 28 sites participating in the T1D Exchange Clinic Network (16) after institutional review board approval at each site. Informed consent was obtained from adult participants and parents/guardians of minors, and assent was obtained from minors as required.

The current study is an ancillary study to the T1D Exchange clinic registry. To be enrolled in the clinic registry, an individual must have had a clinical diagnosis of autoimmune type 1 diabetes, as determined by the physician/study investigator, and either islet cell antibodies present or, if antibodies were negative or unknown, then insulin must have been started at or shortly after diagnosis and used continually thereafter (except in the case of a pancreas or islet cell transplant). Additional eligibility criteria for the current study included age at diagnosis 6 months to <46 years and duration of type 1 diabetes ≥3.0 years. Participants were stratified into subgroups of ~100, based on age at diagnosis (above and below 18 years of age) and duration of disease (3–5, 6–9, 10–19, 20–40, and >40 years).

At study entry, clinical data were collected and nonfasting blood samples were obtained (participants were instructed to eat within 4 h of the blood draw, and insulin was given as usual). All participants with a detectable C-peptide level were invited to undergo a MMTT within 35 days of the screening visit, as previous reports demonstrated high reproducibility of results within this time period (R^2 = 0.96) (3). As per study protocol, up to 10 participants in each age/duration cohort with undetectable nonfasting C-peptide were also invited to undergo MMTT as a control group. MMTT was conducted as previously reported (3) and is described in the Supplementary Data.

Laboratory Measurements

Samples were analyzed at the Northwest Lipid Metabolism and Diabetes Research Laboratories, University of Washington, Seattle, WA. Samples from this study may be available to qualified investigators.

C-Peptide

C-peptide was measured as described in the Supplementary Data. Briefly, C-peptide was tested by a two-site immunoenzymometric assay using a Tosoh 2000 autoanalyzer (Tosoh Bioscience, Inc., South San Francisco, CA). Samples with C-peptide ≥0.017 nmol/L were considered detectable. The interassay CVs for the low, medium, and high C-peptide controls were 3.2%, 1.6%, and 1.8%, respectively.

HbA_{1c}

Measurement of HbA_{1c} levels was performed as described in the Supplementary Data. Briefly, HbA_{1c} measurement was performed by a dedicated analyzer (Tosoh Bioscience, Inc.) using nonporous ion exchange high-performance chromatography to achieve rapid and precise separation of stable HbA_{1c} from other hemoglobin fractions.

Glucose

Measurement of glucose levels was performed as described in the Supplementary Data. Briefly, determination of fasting and stimulated glucose in human samples was performed enzymatically using Roche reagents on a Roche Module P Chemistry autoanalyzer (Roche Diagnostics, Inc., Indianapolis, IN).

Statistical Methods

The proportions of all participants with detectable nonfasting C-peptide (≥0.017 nmol/L) and nonfasting C-peptide ≥0.2 nmol/L were tabulated in subgroups according to diagnosis age and diabetes duration. Univariate and bivariate logistic regression models were performed to assess whether diagnosis age and diabetes duration (as continuous variables) were independently associated with the prevalence of detectable C-peptide. Similar models were conducted to assess the relationship between diagnosis age, diabetes duration, and the prevalence of C-peptide ≥0.2 nmol/L. For validation purposes, this analysis was replicated in a subgroup of participants who were diagnosed at less than 10 years of age or had positive pancreatic autoantibodies at any time (GAD, islet antigen 2, islet cell antibody, or zinc transporter-8).

The random, nonfasting C-peptide results were compared with the stimulated MMTT results by calculating false-positive and false-negative rates. Using these comparative results, covariates were selected to build a logistic regression model that would necessarily adjust the raw prevalence rates obtained from the nonfasting C-peptide results. Since only 269 out of 919 participants completed both the nonfasting and MMTT tests (mainly due to study design and partly due to participants failing to complete the MMTT within the 35-day window), multiple-imputation process was invoked to create a sample set based on available data for those without an MMTT result. This process entailed combining

summary results from 2,000 imputed data sets using logistic regression methods to produce one estimate of prevalence, along with a 95% CI.

Logistic regression was performed to assess whether having detectable C-peptide was associated with the occurrence of one or more severe hypoglycemia events (seizure/coma) in the past year; similar analysis was performed to assess the occurrence of diabetic ketoacidosis events.

All statistical analyses were performed using SAS 9.3 (SAS Institute, Cary, NC). All *P* values are two-sided with a 0.05 significance level.

RESULTS

Characteristics of Study Participants

There were 919 participants enrolled; 54% were female, and 91% were non-Hispanic white (3% non-Hispanic black, 3% Hispanic, and 2% other). The mean ± SD age at time of enrollment into this study was 37.2 ± 18.9 years (range 5–88), median diagnosis age was 14 years (interquartile range 7, 26), and median type 1 diabetes duration was 13 years (interquartile range 6, 30) ranging from 3 to 81 years. Mean ± SD HbA_{1c} was 8.0 ± 1.5% (64 ± 16.4 mmol/mol) (Supplementary Table 1).

Nonfasting C-Peptide According to Age at Diagnosis and Duration of Disease

The overall frequency of detectable nonfasting C-peptide (≥0.017 nmol/L) was 29% (95% CI 26–32%), and the frequency of nonfasting C-peptide ≥0.2 nmol/L was 10% (95% CI 8–12%). The proportion of subjects with detectable nonfasting C-peptide decreased with longer type 1 diabetes duration but was consistently higher when onset had occurred at >18 years of age compared with ≤18 years of age (Fig. 1). When separate univariate logistic regression models were performed, both diagnosis age and type 1 diabetes duration were significantly associated with having detectable nonfasting C-peptide ($P < 0.001$). When both diagnosis age and diabetes duration were included in the model, each factor was independently associated with detectable C-peptide ($P < 0.001$ for both). On average, the odds of having detectable C-peptide were 6% higher for every 1-year increase in diagnosis age, with diabetes duration held constant (odds ratio = 1.06), and the odds of having detectable C-peptide were 7% lower for every 1-year increase in diabetes duration, with diagnosis age held constant (odds ratio = 0.93).

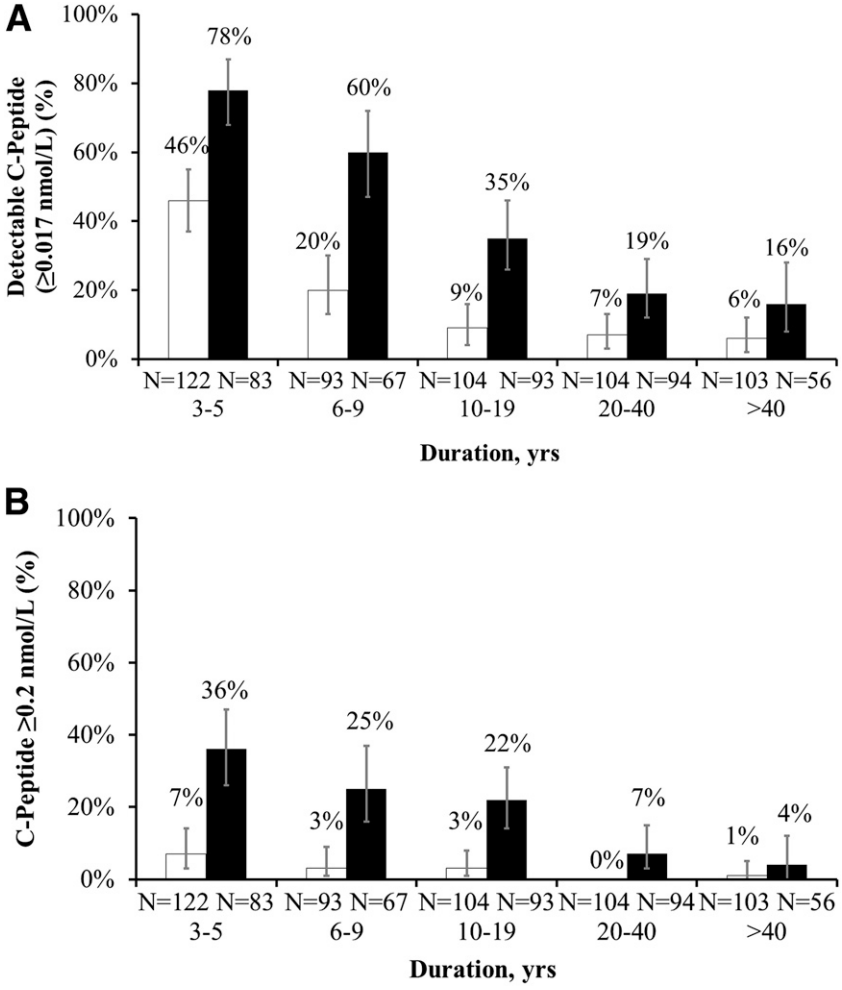

Figure 1—*A*: Proportion of participants with detectable (≥0.017 nmol/L) nonfasting C-peptide, according to age at diagnosis and duration of type 1 diabetes. The white bars represent participants diagnosed with type 1 diabetes at ≤18 years old. The black bars represent participants diagnosed with type 1 diabetes at >18 years old. The gray brackets show exact 95% CIs. Both diagnosis age ($P < 0.001$) and diabetes duration ($P < 0.001$) were independently associated with detectable C-peptide. *B*: Proportion of participants with nonfasting C-peptide ≥0.2 nmol/L, according to age at diagnosis and duration of type 1 diabetes. The white bars represent participants diagnosed with type 1 diabetes at ≤18 years old. The black bars represent participants diagnosed with type 1 diabetes at >18 years old. The gray brackets show exact 95% CIs. Both diagnosis age ($P < 0.001$) and diabetes duration ($P < 0.001$) were independently associated with C-peptide ≥0.2 nmol/L.

Further, while diagnosis at >18 years of age was associated with greater frequency of detectable C-peptide compared with diagnosis at ≤18 years of age (78% vs. 46% with 3–5 years' duration, 60% vs. 20% with 6–9 years' duration, 35% vs. 9% with 10–19 years' duration, 19% vs. 7% with 20–40 years' duration, and 16% vs. 6% with over 40 years' duration), cohorts of both groups had detectable nonfasting C-peptide many years from diagnosis (Fig. 1*A*). Similarly, a higher proportion of individuals diagnosed at >18 years of age had C-peptide concentrations ≥0.2 nmol/L than those diagnosed at ≤18 years of age in each duration bin (36% vs. 7%, 25% vs. 3%, 22% vs. 3%, 7% vs. 0%, and 4% vs. 1%) (Fig. 1*B*). Among those with detectable nonfasting C-peptide, individuals diagnosed with type 1 diabetes at >18 years of age had higher absolute values of C-peptide compared with those diagnosed ≤18 years of age at each duration of disease category (Fig. 2). Frequencies of detectable nonfasting C-peptide and C-peptide ≥0.2 nmol/L were similar when

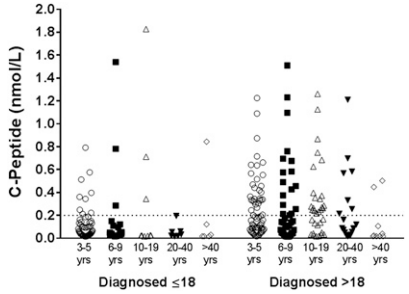

Figure 2—Nonfasting C-peptide values by diagnosis age and duration bins for participants with detectable levels. The white circles represent C-peptide values for participants with 3–5 years' type 1 diabetes duration. The black squares represent C-peptide values for participants with 6–9 years' type 1 diabetes duration. The white triangles represent C-peptide values for participants with 10–19 years' type 1 diabetes duration. The black triangles represent C-peptide values for participants with 20–40 years' type 1 diabetes duration. The white diamonds represent C-peptide values for participants with >40 years' type 1 diabetes duration.

analyses were limited to the validation subgroup (*n* = 714) (Supplementary Fig. 1*A* and *B*).

MMTT-Stimulated C-Peptide

A total of 269 participants underwent MMTT within the 35-day window (Supplementary Fig. 2). Of the 191 who were C-peptide positive at the nonfasting blood draw, 181 were still C-peptide positive on the MMTT, while 10 participants had undetectable stimulated C-peptide levels (false-positive rate 5%) (Table 1). Seventy-eight participants with undetectable C-peptide at the nonfasting blood draw completed the MMTT as negative controls. Out of these, 63 were still C-peptide negative on the MMTT, while 15 participants had detectable stimulated C-peptide levels (false-negative rate 19%). Among the 78 with undetectable nonfasting C-peptide, 4 (25%) of the 16 with blood glucose <100 mg/dL at the nonfasting blood draw had a false-negative result compared with 11 (18%) of the 62 with glucose ≥100 mg/dL (P = 0.49). Applying these false-positive and false-negative rates and using a multiple imputation described in STATISTICAL METHODS above to impute values for participants who did not complete the MMTT within the 35-day window, the true frequency of residual C-peptide was estimated to be 40% (95% CI 33–46%), compared with the uncorrected frequency of 29%. Almost all participants (62/63) with a nonfasting C-peptide ≥0.2 nmol/L also had a peak concentration ≥0.2 nmol/L on the MMTT. Twenty-nine of 128 participants with a random C-peptide level that was detectable, but <0.2 nmol/L, were found to have levels ≥0.2 nmol/L on the MMTT; conversely, 10 had undetectable C-peptide on MMTT. Further, out of the 78 participants who were C-peptide negative at the nonfasting measurement, 14 participants had stimulated C-peptide levels that were detectable but <0.2 nmol/L and one had a stimulated C-peptide concentration ≥0.2 nmol/L (Table 1).

CONCLUSIONS

The American Diabetes Association 2014 Standards of Care describe type 1 diabetes as "β-cell destruction, usually leading to absolute insulin deficiency" (17). This statement has led to the belief among many nonspecialty clinicians that the presence of residual insulin secretion is unexpected in this population. This study of more than 900 participants with type 1 diabetes ranging from 3 to 81 years from diagnosis demonstrated otherwise, with an overall frequency of detectable C-peptide from a random nonfasting C-peptide test of 29%; when adjusted based on MMTT results, the frequency of residual β-cell function may be closer to 40%. We found that 78% of participants diagnosed at >18 years of age and 46% of those diagnosed at ≤18 had residual C-peptide 3–5 years from diagnosis, and 16% of adult-onset and 6% of childhood-onset cases had residual C-peptide even >40 years from diagnosis. Consistent with the previously understood model of disease, the proportion of those with residual C-peptide declined with time from diagnosis; however, this differs considerably whether one was diagnosed as a child or as an adult. This difference was even more striking when evaluating the level of residual nonfasting C-peptide; most of those diagnosed as children who had detectable C-peptide long after diagnosis had markedly lower nonfasting C-peptide values than those with similar disease duration who were diagnosed as adults.

The concept that residual insulin can be present in those with type 1 diabetes is not new. The Joslin Medalist study (10) found detectable insulin secretion in approximately two-thirds of the population of those who had lived with type 1 diabetes for at least 50 years. Additional information about the frequency of residual insulin secretion has been reported from the SEARCH study (13), which involved only children and used only fasting C-peptide values. The DCCT study group recently reported that 10/58 highly selected subjects diagnosed as adults and ~30 years from diagnosis had stimulated C-peptide values >0.03 nmol/L (11). Similarly, combined data from TrialNet studies described insulin secretion in adults and pediatric subjects entered in type 1 diabetes clinical trials, but only within 2 years of diagnosis (8). As in our current study, Barker et al. (15) reported differences in C-peptide according to age at diagnosis. While involving a large number of subjects, that study involved only subjects within 5 years of diagnosis and used noncentralized measurements of fasting C-peptide. More recently, a small study (*N* = 74) also described residual insulin secretion long after diagnosis (14). We designed the current study in part to address the limitations of previous reports. We aimed to obtain data from almost

Table 1—Comparison of nonfasting C-peptide with peak stimulated MMTT C-peptide

	Peak C-peptide during MMTT			
Nonfasting C-peptide (random)	C-peptide ≥0.2 nmol/L	C-peptide 0.017–0.2 nmol/L	C-peptide <0.017 nmol/L	Total
C-peptide ≥0.2 nmol/L	62	1	0	63 (23%)
C-peptide 0.017–0.2 nmol/L	29	89	10	128 (48%)
C-peptide <0.017 nmol/L	1	14	63	78* (29%)
Total	92 (34%)	104 (39%)	73 (27%)	269**

Each cell represents the number of subjects in each category defined by C-peptide value on nonfasting and MMTT tests. *Approximately 10 controls (C-peptide negative) per age/duration subgroup were asked to return for MMTT. **Total number of participants who came in for 1-month MMTT within 35 days of baseline nonfasting test (prespecified visit window).

1,000 subjects from multiple centers across the U.S. in structured cohorts of those diagnosed as children as compared with adults at defined durations of disease. Sample collection was standardized, and measures were centralized. In this way, our data provide robust estimates of residual C-peptide frequency according to disease duration.

Our study does have limitations. The population included here was recruited from pediatric and adult T1D Exchange clinics in the U.S. The population is predominantly Caucasian and non-Hispanic. We cannot exclude selection biases that may have occurred in subject recruitment within centers. We used a well-validated C-peptide assay with a detection limit of 0.017 nmol/L. Other studies have reported results using C-peptide assays with a lower limit of detection (18); thus we cannot exclude that there is an even higher frequency of persistent insulin secretion than reported here. In this cross-sectional study, the relationships of C-peptide and clinical parameters were not clear. After adjusting for diagnosis age and diabetes duration, we found no association between clinical events such as severe hypoglycemia or diabetic ketoacidosis and detectable C-peptide (data not shown), which may be because of the low event rates.

The data have research and clinical implications. The MMTT has been shown to be a highly reproducible and well-tolerated measure of residual insulin secretion in the context of clinical trials (3); however, it is less useful as a routine clinical test. We found that categorical assessment of the presence or absence of C-peptide from a nonfasting random blood draw is a reasonable but not exact measure of the assessment that would be made during an MMTT. Differences between the nonfasting random and MMTT did not appear to be due to low blood glucose levels at the time of the random test. Thus the differences between random and MMTT assessments are likely due to a submaximal stimulation that occurs on a random draw. Indeed, the values obtained from the random test often are lower than those obtained during the MMTT. This suggests that there remains a need for the stimulated test in the context of clinical trial outcome evaluations.

Our data also suggest important differences in the biological process of type 1 diabetes between those diagnosed as children or as adults. While many diagnosed as adults have significant amounts of persistent β-cell function under usual care, the pediatric population may be more likely to derive clinical benefit from trials aiming to preserve β-cell function. These data also support the concept that such trials should be powered separately for each age group.

In the U.S., the Centers for Medicare and Medicaid Services will provide payment for the use of subcutaneous insulin infusion (insulin pumps) for those with type 1 diabetes; however, one criterion for coverage is low or absent C-peptide (19). Our data suggest that this restriction would exclude coverage for at least 10% of type 1 diabetes patients, disproportionally impacting those diagnosed as adults, where almost 20% have C-peptide levels $\geq$0.2 nmol/L. Moreover, many clinicians use the presence of C-peptide as an exclusion criterion for the diagnosis of type 1 diabetes and explain to patients with C-peptide and antibodies that their diagnosis is uncertain. The inconsistencies in diagnosis are likely to confound new initiatives evaluating care and outcomes using ICD-9 or ICD-10 coding and electronic medical records.

In summary, like others, we found that the frequency of detectable residual β-cell function in those with type 1 diabetes is more common than generally assumed. These data reinforce the inadvisability of using C-peptide alone to differentiate between type 1 diabetes and other forms of diabetes. Moreover, our data suggest that random nonfasting assessments of C-peptide may be a reasonable approach to determine the presence or absence of insulin secretion but that stimulated C-peptide testing is needed in the context of clinical trials.

While age of diagnosis is clearly a key variable associated with persistence of β-cell function over time, our data set sets the stage for greater understanding of the heterogeneity of disease within these groupings. The T1D Exchange aims to make data and samples available from this study to the scientific community to unravel immunologic, genetic, and metabolic features that result in such diverse outcomes. Longitudinal follow-up of these individuals is underway to better understand the natural history of insulin secretion in those with long-standing disease and its relationship with clinical outcomes.

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