Distribution of C-Peptide and Its Determinants in North American Children at Risk for Type 1 Diabetes

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OBJECTIVE
To determine basal and stimulated C-peptide percentiles in North American children and adolescents at risk for type 1 diabetes (T1D) and to examine factors associated with this distribution in the Diabetes Prevention Trial–Type 1 (DPT-1).

RESEARCH DESIGN AND METHODS
We included 582 subjects aged 4–18 years at randomization in the DPT-1 trials. A 2-h oral glucose tolerance test (OGTT) was performed at baseline and every 6 months during the 5-year follow-up period. The percentile values of C-peptide after baseline OGTT were estimated according to age, BMI Z score (BMIZ), and/or sex categories. Conditional quantile regression was used to examine the relationship between C-peptide percentiles and various independent variables.

RESULTS
The basal and stimulated C-peptide levels increased significantly as age and BMIZ increased (P < 0.05). Both age and BMIZ had a stronger impact on the upper quartile of C-peptide distributions than the lower quartile. Sex was only significantly associated with stimulated C-peptide. Higher stimulated C-peptide levels were generally observed in girls compared with boys at the same age and BMIZ (P < 0.05). HLA type and number of positive antibodies and antibody titers (islet cell antibody [ICA], insulin autoantibody, GAD65A, and ICA512A) were not significantly associated with C-peptide distribution after adjustment for age, BMIZ, and sex.

CONCLUSIONS
Age-, sex-, and BMIZ-specific C-peptide percentiles can be estimated for North American children and adolescents at risk for T1D. They can be used as an assessment tool that could impact the recommendations in T1D prevention trials.

Type 1 diabetes (T1D) is a metabolic disease characterized by elevated blood glucose levels due to insufficient insulin production (1–3). It results from an autoimmune process that leads to destruction of pancreatic β-cells. C-peptide and insulin are released simultaneously from the pancreas with the cleavage of proinsulin. Measurement of C-peptide production under a standardized condition provides a sensitive assessment of β-cell function (4–8).

C-peptide levels have been used as a surrogate outcome for preserved β-cell function in intervention trials conducted in new-onset patients. Even earlier assessment (i.e., in at-risk subjects) of C-peptide and its precipitating or determinant factors has been used to guide intervention efforts. The distribution of C-peptide levels in children and adolescents at risk for T1D is important for understanding the natural history of β-cell function and for assessing the effectiveness of intervention strategies.
factors is critical. Most previous studies have reported only means and SDs assuming that measurement of C-peptide production follows a normal distribution (9,10). However, C-peptide profiles may follow a nonnormal distribution, which could substantially impact interpretation. When traditional statistical linear regression techniques are deployed such as ordinary least square and general linear model, a departure from normality can result in inaccurate estimates of C-peptide. Accurate risk characterization is critical in the design of prevention trials.

A number of environmental and genetic factors are known to be associated with T1D. Environmental factors, such as exposure to enteroviral infections and cow’s milk, have been identified as potential triggers of T1D in epidemiological and immunological studies (11–13). Previous studies also established that factors, such as age, sex, BMI, relationship to proband, HLA type, and antibody titer levels, were related to progression of clinical T1D onset in children and adolescents at risk (14,15). These factors contribute to the risk for T1D independently or interactively at different pre-diabetes stages. The distribution of C-peptide may or may not depend on one or more of these factors that are linked to clinical disease onset. Taking into account the above observations and considering the importance of early detection of low C-peptide or preservation of C-peptide in subjects at risk for T1D (as the best strategy for the prevention of T1D), we aimed in this study to determine percentiles for basal and stimulated C-peptide in children and adolescents at risk for T1D and to examine factors associated with the distribution of C-peptide using the data from one of the largest T1D prevention trials.

RESEARCH DESIGN AND METHODS

Subjects

The Diabetes Prevention Trial-Type 1 (DPT-1) was a multicenter randomized, controlled clinical study in North America designed to determine whether it is possible to delay or prevent the clinical onset of T1D in individuals with autoimmunity. More than 100,000 nondiabetic relatives of subjects with T1D were screened to detect the presence of islet cell antibodies (ICAs). Individuals found to have ICAs were staged to determine their risk of T1D based on genetic, immunologic, and metabolic characteristics. A total of 711 individuals were randomized into either a parenteral trial or an oral insulin trial according to their risk profiles. These randomized subjects were followed until T1D onset or up to 5 years. Previous analyses showed that the subjects failed to reach the primary end point of preventing diabetes. We analyzed 582 subjects aged 4–18 years at randomization. Among them, 224 (38.5%) subjects were 4–8 years old and 358 subjects (61.5%) were 9–18 years old. There were 350 boys (60.1%) and 232 (39.9%) girls.

Laboratory Measures

All assays including antibody assays were performed as previously described (16). For HLA-DQ typing, DNA was extracted from the buffy coats of peripheral blood leukocytes, and HLA-DQA1 and DQB1 alleles were amplified by PCR with the use of sequence-specific probes. A high-risk HLA genotype was defined as having one of the following haplotype combinations: DQA1*0301-DQB1*0302, DQA1*0501-DQB1*0201, DQA1*04-DQB1*0201, or DQA1*0301-DQB1*0201. No HLA DQB*0602s were included.

At baseline and every 6 months during the follow-up period, an oral glucose tolerance test was done after an overnight fast and blood samples were drawn at −10 and 0 min. An oral glucose load was then administered (1.75 g/kg, maximum 75 g). Blood samples were drawn at 30, 60, 90, and 120 min after glucose consumption. C-peptide levels were measured by radioimmunoassay in the DPT-1 β-cell function core laboratory (Seattle, WA). The basal C-peptide level in the current analysis was calculated as the mean of C-peptide levels at −10 and 0 min. The stimulated C-peptide was analyzed as the peak C-peptide level during a 2-h OGTT test. C-peptide was measured in nanograms per milliliter (1 ng/mL is equal to 0.333 nmol/L).

Statistical Methods

The descriptive statistics of both observed basal and stimulated C-peptide levels at baseline, such as their mean, minimum, median, maximum values, SDs, skewness, and kurtosis, were reported. A Kolmogorov-Smirnov goodness-of-fit test was used to test for the normality of its distribution (17).

A nonparametric approach, conditional quantile regression, was used to examine the relationship between baseline C-peptide percentiles and various independent variables. By extending the exclusive focus of the estimation of conditional mean functions in traditional regression models, the quantile regression approach allows examining of the entire distribution of the variable of interest (C-peptide here) rather than a single measure of the central tendency of its distribution. In addition, the quantile regression approach has its advantages over traditional regression models for its flexibility to allow the covariates to have different impacts at different percentiles of the distribution as well as its robustness with respect to departures from normality and skewed tails because it does not put any distributional assumption beforehand (18–20). The effect of potential covariates, including age categories (≥4 and ≤8 vs. ≥9 and ≤18 years), sex (female vs. male), BMI Z score (BMIz) percentile categories (<85.0 vs. ≥85.0), relationship to proband (offspring, sibling, second degree), HLA type (high vs. low risk), number of positive antibodies, and antibody titer levels, were examined univariately first. Prepubertal subjects were defined as age <9 years (21–23). The significant covariates in the univariate model were then selected as the predictors in a multivariate model to account for the possible variations in determining the distribution of C-peptide. Lastly, the estimated percentile values of C-peptide were reconstructed and refined by the covariates that were both univariately and multivariately related to C-peptide distribution profile.

All tests of significance were two tailed. P ≤ 0.05 was considered statistically significant. Statistical analyses were performed with SAS (version 9.2; SAS Institute, Cary, NC).

RESULTS

Table 1 demonstrates the subjects’ demographics and clinical and laboratory characteristics. The majority of subjects were white (92.71%), had high-risk HLA types (84.54%), and had three or four positive antibodies (84.88%) at baseline. Approximately 23% of subjects in this population were overweight or obese based on their BMIz (≥85.0 percentile).
The mean basal and stimulated C-peptide levels were 1.0 and 4.9 ng/mL, respectively. The median values were 0.6 ng/mL for basal and 3.5 ng/mL for stimulated C-peptide. The median values were less than the (arithmetic) mean values for both basal and stimulated C-peptides, which indicated that the distribution of C-peptide was right skewed. The kurtosis was higher for the basal C-peptide (4.6) than for the stimulated C-peptide (1.6). Higher value of kurtosis indicates a higher and sharper peak. These observations suggest that the C-peptide distributions do not conform to a normal distribution, and a formal Kolmogorov-Smirnov goodness-of-fit test for normality based on skewness and kurtosis rejected the hypothesis that the basal C-peptide or stimulated C-peptide is normally distributed ($P < 0.01$ for both basal and stimulated C-peptide).

Table 2 presents univariate quantile regression analyses. Relationship to proband, number of positive antibodies, ICA titer, GAD65A titer, and ICAS12A titer were not associated with the C-peptide percentiles. Age, BMIZ percentile, HLA type, and insulin autoantibody (IAA) antibody titer were significantly related to the distribution of C-peptide, and these covariates were included in the multivariate models to account for all possible variations of C-peptide distribution. Sex was not associated with basal C-peptide but was significantly associated with stimulated C-peptide in univariate analyses. Therefore, sex was included in the multivariate model for the stimulated C-peptide only.

Table 3 reveals the results from the multivariate model. An age-related significant increase in C-peptide distribution was detected ($P < 0.001$). Sex was associated with stimulated C-peptide. Higher stimulated C-peptide percentiles were generally observed in girls compared with boys at the same age and BMIZ scores ($P < 0.05$). BMIZ scores were significantly associated with both basal and stimulated C-peptide distribution ($P < 0.001$), with no evidence of significant effect modification by either age or sex. As indicated in Fig. 1, both age and BMIZ had a stronger impact on the upper quartile of C-peptide distribution than the lower quartile. HLA type and IAA titer were no longer associated with the percentiles of basal or stimulated C-peptide after adjustment for age, sex, and BMIZ percentile. Further analysis demonstrated that age was significantly inversely related to IAA titer (data not shown). IAA titers were higher in the younger age-group ($P < 0.001$) compared with the older group, which indicates that IAA might be a confounding factor of C-peptide distribution rather than a determinant factor.

Supplementary Table 1 shows the estimated percentile values of basal C-peptide in children and adolescents with T1D ICA autoimmunity according to their age categories and BMIZ categories, respectively. Supplementary Tables 2 and 3 show the percentile values for boys and girls of all age and BMIZ groups combined. Percentile values were calculated for each group, even when the statistical tests indicated lack of differences between certain groups in lower percentiles. For all percentiles, stimulated C-peptide in lower-BMIZ girls was significantly different ($P < 0.03$) from that in high-BMIZ girls at both age periods. For boys, the same pattern was observed.

**CONCLUSIONS**

Previous findings from the DPT-1 study have shown that C-peptide is a good biomarker in predicting T1D onset in children at risk, with a level of prediction ability similar to that of glucose level (24,25). Longitudinal studies have shown that individuals at risk have a prolonged and gradual loss of C-peptide with the persistence of substantial β-cell function until at least 6 months before the onset of clinical disease (9,26,27). We believe that this is the first study to examine factors associated with C-peptide production in children and adolescents at risk for T1D. We found that ICA, IAA, GAD65A, and ICAS12A antibody titers were not significantly associated with C-peptide distribution after adjustment for age, BMIZ, and sex in the samples from DPT-1. This
is consistent with previous studies in children with newly diagnosed T1D (28–30). The relationships to proband or HLA type were also not found to be significant predictors of C-peptide. These data clearly demonstrate that the distributions of basal and stimulated C-peptide in a sample of children and adolescents with autoimmunity depend on BMIZ and age. Subjects with higher BMIZ have higher C-peptide at the considered percentiles than the subjects with lower BMIZ. Likewise, older children have higher C-peptide than children at a younger age. Interestingly, >30% (N = 68) of subjects who progressed to overt T1D at the end of study did not have an absolute decrease in stimulated C-peptide at the time of diagnosis from baseline. Approximately 75% of these subjects who were <9 years old at baseline were progressing through puberty, at which time there is a known increase in insulin production, and a total of 16% of subjects who had lower BMIZ percentile at baseline had increased BMIZ at the time of diagnosis. Thus, the decrease in C-peptide production at diagnosis may be considered not just a loss in absolute terms but also a failure to increase with age or BMIZ (31). A future longitudinal analysis to study the percentile changes before disease onset is warranted.

Our results also demonstrate that boys have lower stimulated C-peptide compared with girls in all age-groups. However, basal C-peptide was not sex dependent. This may suggest that boys with autoimmunity are less likely to progress to overt disease than comparable girls and that the pathogenesis of T1D among boys may be slower compared with girls. Overall β-cell function may need to be further reduced in boys than in girls to progress to T1D (32,33). In addition, girls may have less insulin sensitivity owing to higher BMIZ than boys at the same age.

The estimated values in Supplementary Tables 4–6 provide a powerful tool for the interpretation of C-peptide in children at different BMIZ categories and age-groups. Based on these values, careful attention to children with C-peptide values that fall on the 10th and 25th percentiles, according to their BMIZ classification and age, becomes important in the identification of subgroups of children progressing to clinical T1D. For example, at the 25th percentile of the basal distribution, the children between 9 and 18 years of age exceed

| Table 2—Univariate quantile regression model for predicting C-peptide percentiles | Basal C-peptide | Stimulated C-peptide |
|---|---|---|
| 25th percentile | 50th percentile | 75th percentile | 25th percentile | 50th percentile | 75th percentile |
| Sibling | 0.25 | 0.11 | 0.54 | 0.18 | 1.00 | 0.46 |
| Offspring | 1.00 | 0.50 | 0.55 | 0.60 | 0.61 | 0.44 |
| Second degree | 0.08 | 0.40 | 0.12 | 1.00 | 0.15 | 0.84 |
| Number of positive antibodies | | | | | |
| 1 vs. 4 | 0.06 | 0.10 | 0.11 | 1.00 | 0.27 | 0.85 |
| 2 vs. 4 | 0.49 | 1.00 | 0.57 | 0.32 | 0.51 | 0.19 |
| 3 vs. 4 | 0.33 | 0.09 | 1.00 | 1.00 | 0.65 | 0.30 |
| IAA titer | 0.13 | 0.05 | 0.29 | 0.16 | <0.001 | 0.02 |
| ICA titer | 0.62 | 1.00 | 0.84 | 0.25 | 0.66 | 0.21 |
| GAD65A titer | 1.00 | 1.00 | 0.63 | 0.00 | 1.00 | 0.54 |
| ICAS12 titer | 0.47 | 0.53 | 0.60 | 1.00 | 0.63 | 0.71 |
| HLA (high vs. low risk) | 0.05 | 0.05 | 0.09 | 0.54 | 0.02 | 0.31 |
| Sex (female vs. male) | 0.23 | 0.10 | 0.54 | 0.11 | <0.001 | 0.01 |
| BMIZ percentile (<85.0 vs. ≥85.0) | 0.01 | 0.00 | 0.00 | <0.001 | <0.001 | <0.001 |
| Age (4–8 vs. 9–18 years) | <0.001 | 0.00 | 0.00 | <0.001 | <0.001 | <0.001 |

Data are P values.

| Table 3—Multivariate quantile regression model for predicting C-peptide percentiles (coefficient and its 95% CI) | Basal C-peptide | Stimulated C-peptide |
|---|---|---|
| 25th percentile | 50th percentile | 75th percentile | 25th percentile | 50th percentile | 75th percentile |
| Basal C-peptide | | | | |
| HLA (low vs. high risk) | 0.00 | −0.15 | 0.15 | 0.10 | −0.02 | 0.22 | 0.10 | −0.13 | 0.33 |
| IAA titer | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| BMIZ percentile (<85.0 vs. ≥85.0) | −0.24 | −0.33 | −0.16 | −0.31 | −0.43 | −0.19 | −0.55 | −0.72 | −0.38 |
| Age (4–8 vs. 9–18 years) | −0.34 | −0.43 | −0.25 | −0.40 | −0.48 | −0.33 | −0.60 | −0.72 | −0.48 |
| Stimulated C-peptide | | | | |
| Sex (female vs. male) | 0.58 | 0.27 | 0.89 | 0.50 | 0.10 | 0.90 | 0.79 | 0.37 | 1.20 |
| HLA (low vs. high risk) | 0.26 | −0.09 | 0.60 | 0.26 | −0.29 | 0.81 | 0.27 | −0.66 | 1.20 |
| IAA titer | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| BMIZ percentile (<85.0 vs. ≥85.0) | −1.00 | −1.32 | −0.68 | −1.05 | −1.54 | −0.56 | −1.85 | −2.32 | −1.39 |
| Age (4–8 vs. 9–18 years) | −1.28 | −1.52 | −1.04 | −1.50 | −1.89 | −1.10 | −1.90 | −2.29 | −1.52 |
the basal C-peptide values of 1.00 ng/mL, identified as the cutoff point for increased risk of T1D among higher-BMIZ children. Similarly, at ages 9–18 years, the children with lower BMIZ achieved the 0.75 ng/mL cutoff point in the 25th percentile of the basal C-peptide distribution and 0.50 ng/mL cutoff point in the 10th percentile. Therefore, the cutoff point for C-peptide to classify subjects as having a loss of β-cell function may be different depending on their age, BMIZ, and/or sex.

Standard linear regression models, such as ordinary least square, are extensively used in statistical analyses. Despite their popularity, these conditional mean models have several limitations. When interest is in the percentiles of the conditional distribution rather than the mean, standard regression models may fail to provide the desired information because the assumption of normally distributed residuals with constant variance may not be justified. Standard regression models are sensitive to outliers and can lead to unrealistic models if outliers are present in the data set. This is especially a problem if the sample size is moderately small and the error distribution is heavy tailed (17,18). Quantile regression overcomes these limitations of standard linear regression. It is robust in handling extreme value points and outliers for the outcome of interest. More importantly, it provides a more complete understanding of the impact of covariates on the

Figure 1—Effect of age, BMIZ, and/or sex on C-peptide by quantile. A: Effect on basal C-peptide (age 4–8 vs. 9–18 years, BMIZ < 85.0 vs. ≥85.0 percentile) (estimated parameter by quantile for baseline fasting C-peptide with 95% CI). B: Effect on stimulated C-peptide (sex female vs. male; age 4–8 vs. 9–18 years; BMIZ < 85.0 vs. ≥85.0 percentile) (estimated parameter by quantile for baseline peak C-peptide with 95% CI).
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