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Early and late C-peptide responses during oral glucose tolerance testing are oppositely predictive of type 1 diabetes in autoantibody-positive individuals

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Abstract

We examined whether the timing of the C-peptide response during an oral glucose tolerance test (OGTT) in relatives of patients with type 1 diabetes (T1D) is predictive of disease onset. We examined baseline 2-h OGTTs from 670 relatives participating in the Diabetes Prevention Trial-Type 1 (age: 13.8 ± 9.6 years; body mass index z score: 0.3 ± 1.1; 56% male) using univariate regression models. T1D risk increased with lower early C-peptide responses (30–0 min) (χ^2 = 28.8, $P < 0.001$), and higher late C-peptide responses (120–60 min) (χ^2 = 23.3, $P < 0.001$). When

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AUTHOR CONTRIBUTIONS

The study was conceived by J.M.S., who also performed the analyses, interpreted the data and edited the manuscript. H.M.I. acquired and interpreted the data and drafted and edited the manuscript. All authors critically reviewed the manuscript and approved the final version. J.M.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

CONFLICT OF INTEREST

The authors have no conflict of interest to report.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

both responses were included in a proportional hazards model, they remained independently and oppositely associated with T1D, with a stronger overall association for the combined model than either response alone ($\chi^2 = 41.1$; $P < 0.001$). Using receiver operating characteristic curve analysis, the combined early and late C-peptide response was more accurately predictive of T1D than area under the curve C-peptide ($P = 0.005$). Our findings demonstrate that lower early and higher late C-peptide responses serve as indicators of increased T1D risk.

Keywords

C-peptide; oral glucose tolerance test; type 1 diabetes

1 | INTRODUCTION

Previous studies suggest that partitioning C-peptide responses during a 2-h oral glucose tolerance test (OGTT) provides important information for assessing the natural history of the metabolic progression to type 1 diabetes (T1D) among autoantibody-positive (Ab+) relatives of individuals with the disease. Longitudinal analyses of Ab+ relatives of people with T1D showed that overall 2-h C-peptide measures [such as area under the curve (AUC) C-peptide] from OGTTs decrease gradually until 6 months before the diagnosis of T1D, followed by a marked decline.[1] A subsequent analysis suggested that partitioning C-peptide responses according to time intervals provides more insight into the natural history of C-peptide loss, with early C-peptide responses (30–0 min C-peptide difference) decreasing, and later C-peptide responses (sum of each of the differences of the 30-min C-peptide value from the 60-, 90-and 120-min values) increasing within 2 years of diagnosis.[2] However, it remains unknown to what extent this pattern of C-peptide responsiveness at baseline is predictive of T1D. Therefore, we examined whether partitioning the timing of the C-peptide response to an oral glucose load at a baseline exam is more predictive of the time to a diagnosis of T1D compared with the AUC C-peptide. In addition, we investigated the basis for the late response.

2 | MATERIALS AND METHODS

We analysed data from relatives of individuals with T1D (aged 1–45 years) who participated in the Diabetes Prevention Trial-Type 1 (DPT-1) with complete 2-h OGTT data. The DPT-1 study has been previously described in detail.[3] Briefly, participants were monitored with 2-h OGTTs every 6 months for the diagnosis of diabetes. Glucose and C-peptide levels were measured fasting and every 30 min. American Diabetes Association criteria for the diagnosis of diabetes were used for the interpretation of OGTTs.[4] If an OGTT was in the diabetic range, a confirmatory OGTT was performed (unless otherwise clinically contraindicated). The date of diagnosis was based on the first OGTT results. A diagnosis could also be made according to the clinical presentation.

The early C-peptide response was defined as the 30–0 min C-peptide values (nmol/L). To avoid overlap in the 30-min C-peptide time point previously used for the definition of the later C-peptide response, we used the 120–60 min C-peptide as a measure of the late response. The AUC was calculated using the trapezoidal rule with the mean values of AUC

(/120 min) being presented. Plasma C-peptide levels were measured by radioimmunoassay, as has been previously described.[1] Proportional hazards regression, with and without covariate adjustments, was used to assess associations. For certain analyses the early and late C-peptide responses were combined to form a single variable using their coefficients from a proportional hazards model that included both variables.

$$\text{Combined} = \; - \; - 0.6225 \times \text{early response} + 0.6163 \times \text{late response}$$

The hazard ratio (HR) for each response is based on a 1 nmol/L difference, with a ratio of <1 indicative of lower risk and >1 indicative of greater risk. Receiver operating characteristic curves (ROC) were assessed according to time of follow-up with proportional hazards regression models. Pearson correlation was also utilized.

The data analysed or generated during the study are available on request from the authors.

3 | RESULTS

Baseline 2-h OGTTs from 670 DPT-1 participants [mean ± SD age:13.8 ± 9.6 years; body mass index (BMI) z-score: 0.3 ± 1.1; 56% male] were analysed. In total, 241 progressed to T1D. The mean duration of follow-up was 3.8 ± 1.7 years.

Table 1 includes univariate proportional hazards regression models for the early C-peptide response, late C-peptide response and AUC C-peptide. The risk for a clinical T1D diagnosis was related significantly and inversely to the early C-peptide response ($P < 0.0001$ for HR). In contrast, another univariate regression model showed that the risk for T1D was significantly and positively related to the 120–60 min C-peptide difference ($P < 0.0001$ for HR). (Because of the differing directions of association, a 1 nmol/L increase in the early C-peptide response was associated with a near halving of the HR, while a 1 nmol/L increase in the late C-peptide response was associated with an approximate doubling of the HR.) Each C-peptide response (i.e., early and late responses) was at least as associated with T1D development [$\chi^2 = 28.8$ ($P < 0.0001$) and $\chi^2 = 23.3$ ($P < 0.0001$), respectively] as the AUC C-peptide ($\chi^2 = 20.4$), which is a standard overall C-peptide response measure. As also shown in Table 1, all of the associations persisted with adjustments for age and BMI z-score.

The early and late C-peptide responses were independently and oppositely associated with T1D in a model, including both variables: inverse for the early C-peptide response [HR: 0.54 (0.41–0.70); $P < 0.0001$] and positive for the late C-peptide response [HR: 1.85(1.35–2.53); $P < 0.0001$]. These associations persisted ($P < 0.0001$) for both with adjustments for age and BMI z-score. In addition, the overall association was stronger in the combined model (unadjusted $\chi^2 = 41.1$, $P < 0.0001$). The association was further improved with the inclusion of age and BMI z-score in the model ($\chi^2 = 67.6$, $P < 0.0001$). Table S1 (see Supporting Information) shows the mean ± SD C-peptide values at each OGTT time point.

Table 2 shows that the values of prediction accuracy indicators were similar between the AUC C-peptide and each of the early and late C-peptide responses. However, the values

tended to improve for a combined variable that included both the early and late C-peptide responses (based upon proportional hazards regression coefficients).

We performed an ROC analysis to assess further the accuracy of prediction when OGTT C-peptide responses are partitioned into early and late responses. Table S2 (see Supporting Information) provides areas under the ROC for the C-peptide measures. The areas under the ROC were significantly higher for the 30–0 min C-peptide ($P = 0.039$), and for the 30–0 min C-peptide combined with the 120–60 min C-peptide ($P = 0.005$), than for the AUC C-peptide.

To explain why a high late C-peptide response is predictive of greater T1D risk, we examined the association between the sum of glucose levels from 60 to 120 min and the 120–60 min C-peptide response. The 120–60 min C-peptide response was positively associated with the sum of glucose levels from 60 to 120 min ($r = 0.42$, $P < 0.0001$) (Figure S1; see Supporting Information). Moreover, there was a negative association between the 120–60 min C-peptide and 30–0 min C-peptide ($r = -0.29$, $P < 0.0001$) (Figure S2; see Supporting Information). When we also assessed the association between the early C-peptide response and the glucose sum from 60 to 120 min, a negative association ($r = -0.23$, $P < 0.0001$) was observed.

As the oral and parenteral insulin modalities could have influenced the findings in this study, we tested for interactions between treatment with insulin and the C-peptide measures. There were no significant interactions.

4 | DISCUSSION

The development of T1D was predicted by low early and high late C-peptide responses at baseline OGTTs in Ab+ relatives of individuals with T1D who were initially non-diabetic. The 30–0 min C-peptide difference and the 120–60 min C-peptide difference were each at least as predictive as the AUC C-peptide, and their prediction improved when they were included in combination. This was evident in both the regression and the ROC analyses. These findings are consistent with the changes in those responses during the progression to T1D in longitudinal studies.[2]

The practical value of using the combined early and late C-peptide responses (the higher the value, the greater the risk) versus using the standard AUC C-peptide measure (the lower the value, the greater the risk) is evident from the following example. For the combined variable, the 5-year T1D risk estimate was 68% for the highest risk quartile, while the estimate for the lowest risk quartile was 31%. For the AUC C-peptide the 5-year estimate for the highest risk quartile was 60%, whereas the estimate for the lowest risk quartile was 36% (Table S3; see Supporting Information). The wider separation between the highest risk and lowest risk quartiles of the combined variable suggests that it is a better indicator of the risk for T1D than the AUC C-peptide. This is supported by the greater log-rank χ^2 for the combined variable evident in Table S3.

In assessing the metabolic effect of timing of C-peptide peaks, we observed that a lower early C-peptide response was associated with higher glucose levels during the second hour

of the OGTT and that the latter was associated with a higher late C-peptide response. This suggests that the greater T1D risk associated with the late C-peptide response is a function of a deficient early C-peptide response, resulting in higher late glucose levels and a compensatory higher late C-peptide response. Differences in changes of early and late C-peptide response phases during progression are consistent with the longitudinal studies,[1,2] and with studies of impaired glucose tolerance and type 2 diabetes.[5–7]

The findings from partitioning the C-peptide response into early and late phases have several implications. Clinically, an appreciation of the different phases of the C-peptide response to an oral glucose challenge could potentially provide a more targeted approach for intervention and prevention therapies, as well as provide more physiological treatment approaches that further mimic normal timed insulin secretion of individuals at the onset of T1D. From a research perspective, partitioning should offer more insights than overall measures of the C-peptide response, such as the AUC C-peptide, for assessing β-cell function deterioration during the progression to T1D. Moreover, partitioning the C-peptide response provides additional predictive value of the disorder compared with the standard AUC C-peptide measure.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1

Cox regression models with HR and 95% CI for associations of progression to type 1 diabetes with individual C-peptide responses

	Without adjustments			With adjustments for age and BMI z-score		
	HR (95% CI)	***P*-value**	**χ^2**	**HR (95% CI)**	***P*-value**	**χ^2**
30–0 min C-peptide	0.49 (0.38–0.63)	<0.0001	28.8	0.49 (0.37–0.64)	<0.0001	25.8
120–60 min C-peptide	2.05 (1.53–2.75)	<0.0001	23.3	2.15 (1.59–2.92)	<0.0001	24.6
AUC C-peptide	0.53 (0.40–0.70)	<0.0001	20.4	0.66 (0.49–0.89)	<0.0001	7.4

Abbreviations: AUC, area under the curve; BMI, body mass index; CI, confidence intervals; HR, hazard ratios.

TABLE 2

Indicators of prediction accuracy using highest risk and lowest risk categories (by medians) of C-peptide distributions (n = 670 for full cohort)

	AUC	Early response	Later response	Early + later response
Sensitivity	145/241 (60.2%)	148/241 (61.4%)	150/241 (62.2%)	156/241 (64.7%)
Specificity	238/429 (55.5%)	238/429 (55.5%)	241/429 (56.2%)	250/429 (58.3%)
Likelihood ratio (+)	1.35	1.35	1.42	1.55
Likelihood ratio (−)	0.72	0.70	0.67	0.61
Positive predictive value	145/336 (43.2%)	148/339 (43.7%)	150/338 (44.4%)	156/335 (46.6%)
Negative predictive value	238/334 (71.3%)	238/331 (71.9%)	241/332 (72.6%)	250/335 (74.6%)
Hazard ratio (95% CI)[a]	1.59 (1.23, 2.05)*	1.71 (1.32, 2.22)*	1.90 (1.47, 2.47)*	2.10 (1.62, 2.74)*

Abbreviations: AUC, area under the curve; CI, confidence intervals.

*$P < 0.001$;

[a]Highest category vs. lowest risk category.