

**Associations of HbA1c with the Timing of C-peptide Responses during the Oral Glucose Tolerance Test at the Diagnosis of Type 1 Diabetes**

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**Running Title: HbA1c associations with C-peptide timing**

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### Abstract

Background: In new onset type 1 diabetes (T1D), overall C-peptide measures such as area under the curve (AUC) C-peptide and peak C-peptide are useful for estimating the extent of  $\beta$ -cell dysfunction, and for assessing responses to intervention therapy. However, measures of the timing of C-peptide responsiveness could have additional value.

Objectives: We assessed the contribution of the timing of C-peptide responsiveness during oral glucose tolerance tests (OGTTs) to HbA1c variation at T1D diagnosis.

Methods: We analyzed data from 85 individuals <18 years with OGTTs and HbA1c measurements at diagnosis. Overall [AUC and peak C-peptide] and timing measures [30-0 minute C-peptide (early); 60 to 120 minute C-peptide sum-30 minutes (late); 120/30 C-peptide; time to peak C-peptide] were utilized.

Results: At diagnosis, the mean ( $\pm$ SD) age was 11.2 $\pm$ 3.3 years, BMI-z was 0.4 $\pm$ 1.1, 51.0% were male and the HbA1c was 43.54 $\pm$ 8.46 mmol/mol (6.1 $\pm$ 0.8%). HbA1c correlated inversely with the AUC C-peptide ( $p$ <0.001), peak C-peptide ( $p$ <0.001), early and late C-peptide responses ( $p$ <0.001 each), and 120/30 C-peptide ( $p$ <0.001). Those with a peak C-peptide occurring at d60 minutes had higher HbA1c values than those with peaks later ( $p$ =0.003). HbA1c variance was better explained with timing measures added to regression models ( $R^2$ =11.6% with AUC C-peptide alone;  $R^2$ =20.0% with 120/30 C-peptide added;  $R^2$ =13.7% with peak C-peptide alone,  $R^2$ =20.4% with timing of the peak added). Similar associations were seen between the 2-hr glucose and the C-peptide measures.

Conclusions: These findings show that the addition of timing measures of C-peptide responsiveness better explains HbA1c variation at diagnosis than standard measures alone.

Keywords: type 1 diabetes, C-peptide, glycemia, OGTT, HbA1c

Abbreviations:

120/30 C-peptide: 120/30 minute C-peptide ratio

T1D: type 1 diabetes

OGTT: oral glucose tolerance test

MMTT: Mixed meal tolerance test

CGM: continuous glucose monitor

## **Introduction**

The area under the curve (AUC) C-peptide and peak C-peptide, commonly employed measures of overall C-peptide levels during oral glucose tolerance tests (OGTTs), have been used as markers of  $\beta$ -cell function in the peri-diagnostic period of type 1 diabetes (T1D). However, it is unclear whether such measures are optimal, since they do not take insulin secretory patterns into

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account. Measures of the timing of C-peptide responsiveness have been shown to change during the progression to T1D (1). In that report, the early (30-0 minute) C-peptide response progressively declined from approximately two years prior to until the time of diagnosis, while the late [(60+90+120 minute C-peptide)-30 minutes] C-peptide response progressively increased (1). However, to our knowledge, no studies have yet described the timing of C-peptide responses at diagnosis and how this timing may relate to glycemia. Thus, our objective in this report was to examine associations of glycemia, primarily as indicated by HbA1c, with measures of the timing of C-peptide responsiveness at the diagnosis of T1D. Moreover, we sought to determine whether the addition of those timing measures to standard overall C-peptide measures (such as the AUC C-peptide) in multivariable models helps to explain HbA1c variance.

It has been difficult to assess C-peptide responsiveness at diagnosis in the community, since insulin is almost always administered at that time, and may interfere with endogenous insulin secretory patterns. However, data from the Diabetes Prevention Trial-Type 1 (DPT-1) provides the opportunity for such assessments. In that study, a large proportion of individuals were diagnosed by OGTT, prior to the clinical administration of insulin; many also had HbA1c measurements at diagnosis. We have, therefore, utilized these features of DPT-1 to improve our understanding of how glycemia relates to C-peptide responsiveness at diagnosis.

## **Methods**

The DPT-1 study has been previously described (2). Participants (relatives of persons with type 1 diabetes, ages 1–45 years) were monitored with 2-hr OGTTs bi-annually for diagnosis of diabetes. ADA criteria for the diagnosis of diabetes were used for the interpretation of OGTTs (3). Glucose and C-peptide were measured fasting and every 30 minutes. If an OGTT was in the diabetic range, a confirmatory OGTT was performed (unless otherwise contraindicated). The date of diagnosis was based on the first OGTT, which was used for the following analyses.

DPT-1 participants (n=85) <18.0 years of age at diagnosis with complete OGTT data and a HbA1c measurement performed simultaneously at diagnosis were included in the analysis. C-peptide and glucose assays were performed as previously described (2). Plasma glucose was measured by the glucose oxidase method. C-peptide levels were determined by radioimmunoassay. Measurable C-peptide was considered  $\geq 0.07$  nmol/L ( $\geq 0.2$  ng/ml) because this was the lowest level detectable by that method. HbA1c was measured using the VARIANT (Bio-Rad) instrument. The measurable range for this instrument was 16-162 mmol/mol (3.6 – 17.0%), with normal levels being  $\leq 44$  mmol/mol ( $\leq 6.2\%$ ). The AUC C-peptide measure was calculated using the trapezoidal rule with the mean values of AUC (/120 min) being presented.

Associations between HbA1c and OGTT C-peptide indices at diagnosis were assessed through correlation and multivariable regression. To examine the association of HbA1c with the timing of C-peptide secretion, early and late C-peptide responses were utilized, as previously described (1). The ratio of the 120-minute over 30-minute C-peptide (120/30 C-peptide) and timing of the peak C-peptide (occurring at  $\leq 60$  vs.  $>60$  minutes) were used as measures of relative timing.

Multivariable linear regression models were utilized to determine whether adding measures of relative timing of C-peptide responsiveness would better account for HbA1c variance than overall C-peptide indices. Since BMI-z and age are known to influence C-peptide responses (4), linear regression analyses were performed with BMI z-score and age included as covariates.

The likelihood ratio test was utilized to test the statistical significance of the contribution to the  $R^2$  from adding C-peptide covariates to linear regression models. Squared partial correlations were used to examine the individual contributions of the covariates in explaining HbA1c variance. Please note that although the sum of partial correlations and the overall  $R^2$  of a model can be similar in multivariable models, they are not identical.

## **Results**

The mean ( $\pm$ SD) age of participants was  $11.2\pm 3.3$  years and the BMI z-score was  $0.4\pm 1.1$ ; 51% were male. HbA1c values at diagnosis averaged  $43.54\pm 8.46$  mmol/mol ( $6.1\pm 0.8\%$ ). Metabolic characteristics of the participants at diagnosis are indicated in Table 1.

### **Associations of HbA1c with overall C-peptide responses:**

HbA1c was inversely correlated with measures of overall C-peptide responsiveness: AUC C-peptide ( $r=-0.34$ ;  $p<0.001$ ); peak C-peptide ( $r=-0.37$ ;  $p<0.001$ ).

### **HbA1c associations after partitioning the timing of C-peptide responses:**

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There were significant inverse correlations of HbA1c with both the early and late C-peptide responses ( $r=-0.34$  and  $-0.38$ , respectively;  $p<0.001$  for both), Table 2. These associations are demonstrated in Figure 1A and B, in which HbA1c values are compared among the lowest, the middle and the highest tertiles for the early and late C-peptide distributions (early response:  $47.70\pm 10.66$  for lowest vs.  $38.72\pm 4.26$  mmol/mol for highest [ $6.5\pm 1.0$  vs.  $5.7\pm 0.4\%$ ],  $p<0.001$ ; late response:  $47.54\pm 10.46$  for lowest vs.  $39.65\pm 5.10$  mmol/mol for highest [ $6.5\pm 1.0$  vs.  $5.8\pm 0.5\%$ ],  $p=0.001$ ).

Associations of HbA1c with the relative timing of C-peptide responses:

We examined HbA1c associations with the relative timing of C-peptide responsiveness. There was an inverse correlation between HbA1c and the 120/30 C-peptide ( $r=-0.40$ ;  $p<0.001$ ). HbA1c values were significantly greater in the lowest 120/30 C-peptide tertile than in the highest tertile ( $48.20\pm 10.16$  vs.  $40.36\pm 5.25$  mmol/mol [ $6.6\pm 0.9$  vs.  $5.8\pm 0.5\%$ ],  $p=0.001$ ) (Figure 1C).

Also apparent was the influence of the relative timing of the C-peptide response when we examined the association of HbA1c with the timing of the peak C-peptide (Figure 1D). Those with a peak C-peptide at d60 minutes ( $n=27$ ) had higher HbA1c values than those with a peak C-peptide at  $>60$  minutes ( $n=58$ ) ( $48.03\pm 9.80$  vs.  $41.45\pm 6.90$  mmol/mol [ $6.5\pm 0.9$  vs.  $5.9\pm 0.6\%$ ],  $p=0.003$ ).

Supplemental tables 1-4 show comparisons of OGTT indices between the lowest and highest tertiles of the C-peptide indices in Figure 1.

### The use of the timing of the C-peptide response to account for HbA1c variance

We utilized multivariable regression models to assess whether adding measures of the timing of C-peptide responsiveness would better account for HbA1c variance. Table 3 shows overall and partial  $R^2$  values for associations of HbA1c with C-peptide indices as covariates in the multivariable regression models, with and without the inclusion of BMI z-score and age. As indicated for the partial  $R^2$  indices, HbA1c was significantly associated with each of the C-peptide indices in all models (range:  $p < 0.001$  to  $p = 0.013$ ). Within the models, the contribution of the measures in explaining variance tended to be similar.

When timing variables of C-peptide secretion were added to overall measures in Model A (120/30 C-peptide added to AUC C-peptide) and Model B (peak C-peptide after 60 min added to peak C-peptide), the contributions to the  $R^2$  were statistically significant in both the unadjusted and adjusted models ( $p < 0.05$  for all). When both variables were measures of timing (i.e., absent overall measures) in Model C (early C-peptide and 120/30 C-peptide) and Model D (early C-peptide and late C-peptide), all contributed significantly to the  $R^2$  in the unadjusted and adjusted models ( $p < 0.01$  for all).

### Associations of the 2-hr glucose with C-peptide measures:

Since HbA1c values at diagnosis were indicative of glycemia for several months prior to diagnosis, we assessed whether the association of glycemia with the timing of the C-peptide response was also evident within the same OGTT at diagnosis. Associations were therefore

examined between the 2-hr glucose (designated as the measure of glycemia post-glucose load) and C-peptide indices. Similar to HbA1c, the 2-hr glucose correlated inversely with both early and late C-peptide responses ( $r=-0.43$  and  $r=-0.46$  respectively;  $p<0.001$ ) for both. There was again an inverse correlation with the 120/30 C-peptide ( $r=-0.51$ ;  $p<0.001$ ). When the early C-peptide response and the 120/30 C-peptide were included as independent variables in a regression model, 43.0% of the 2-hr glucose variance was explained. The AUC C-peptide alone accounted for 16.4% of the 2-hr glucose variance.

## **Discussion**

This study is the first to examine the relationship of HbA1c at diagnosis with measures of the timing of C-peptide responses. HbA1c was at least as associated with C-peptide measures of timing and relative timing at diagnosis as with the AUC and peak C-peptide. When C-peptide measures of timing and relative timing were added to the overall measures, appreciably more HbA1c variance was explained. The lower HbA1c values associated with a greater late C-peptide response, a higher 120/30 C-peptide, and a peak C-peptide occurring after 60 minutes suggest the importance of maintaining insulin secretion during the latter part of the OGTT, and the need for its quantitative assessment. The AUC C-peptide and the peak C-peptide do not specifically capture this important aspect of  $\beta$ -cell function. We also observed appreciable associations

between the 2-hr glucose and the C-peptide timing measures. These findings are relevant, since the 2-hr glucose is a major diagnostic criterion for type 1 diabetes.

Our findings also showed that besides the specific effect of adding C-peptide timing indices to overall measures, timing indices can provide appreciable information with regard to glycemia even in the absence of overall measures (i.e., AUC and peak C-peptide levels). The combination of the early C-peptide response and the 120/30 C-peptide in a model resulted in an appreciable  $R^2$  value, as seen in table 3. The contributions in explaining glycemia by the additions of the C-peptide timing indices should be considered in the context of the low range of C-peptide values at the diagnosis of type 1 diabetes. Those indices help to discern even subtle changes of C-peptide in that range. Although such changes might be small in overall magnitude, they could have a substantial influence on glycemia.

Other studies such as The Environmental Determinants of Diabetes in the Young (TEDDY) and the Diabetes Autoimmunity Study in the Young (DAISY) studies have assessed  $\beta$ -cell function in children with T1D near diagnosis. In both studies, (5, 6), researchers assessed residual  $\beta$ -cell function post-diagnosis using serial MMTTs. However, neither study assessed measures of timing of C-peptide during a diagnostic OGTT.

The results further suggest that the timing and relative timing of the C-peptide response should be considered in developing endpoints for  $\beta$ -cell preservation trials. Since measures assessing the timing of C-peptide secretion have been used as predictor(s) of islet allograft dysfunction in islet

transplant studies (7), such measures could possibly also be useful for assessing residual  $\beta$ -cell function in new onset clinical trials.

Clinically, an understanding of the pattern of insulin responsiveness to a glucose challenge could provide insights into the heterogeneity of new onset type 1 diabetes, and potentially provide more physiologic approaches for individualized treatment paradigms.

The range of HbA1c values and the differing patterns of C-peptide responsiveness could be reflective of the variability of  $\beta$ -cell function at the diagnosis of type 1 diabetes, even among those diagnosed by OGTT. However, it is unclear to what extent the differences were a function of the timing of the OGTT during progression or due to the heterogeneity of type 1 diabetes. It is important to determine whether more preserved C-peptide secretion at diagnosis persists, since those with even modest residual  $\beta$ -cell function have a lower risk of microvascular complications and hypoglycemia (8-10).

The study has limitations. HbA1c levels might not have reflected actual concurrent associations between glucose and C-peptide at diagnosis, since HbA1c is indicative of glycemia over several months. However, associations were similar for the 2-hr glucose of the diagnostic OGTT. Mixed meal tolerance tests (MMTTs) have been used in insulin preservation trials of new onset patients, and OGTT timing measures are not necessarily applicable to MMTTs. Still, the evidence for the importance of sustaining later insulin secretion would appear likely to translate to MMTTs.

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Future investigations of the timing of C-peptide responses appear warranted. Associations of glycemia with such measures should be performed in other cohorts. C-peptide timing measures could be assessed as predictors of T1D in natural history and prevention trials. Those measures could also be assessed as endpoints indicative of C-peptide loss in the peri-diagnostic period. Although MMTTs are not performed at diagnosis, the timing of C-peptide responsiveness might be examined in MMTTs near diagnosis. Finally, it would be of interest to study associations of continuous glucose monitoring (CGM) indices with the timing of C-peptide responses in OGTTs or MMTTs performed in close proximity to the CGM.

In conclusion, overall measures of C-peptide secretion, the AUC C-peptide and the peak C-peptide, are not fully indicative of  $\beta$ -cell secretory function at diagnosis. The consideration of the timing of insulin secretion following a glucose challenge would allow for a better characterization of  $\beta$ -cell dynamic function at the diagnosis of type 1 diabetes.

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### **Contribution Statement**

JMS conceptualized the analysis, analyzed and interpreted the data. HMI contributed to the design, interpreted the data, and wrote the manuscript. C E-M, LD, DJB, IL, ES, DB, KH; LR, JSS and JPP all contributed to the design, interpreted the data and reviewed/edited the manuscript.

HMI is the guarantor of this work, and all authors provided final approval of the manuscript prior to publishing.

### **Data availability**

The data was analyzed or generated during the study and is available on request from the authors.

### **Duality of Interest**

The authors declare that there is no duality of interest associated with this manuscript.

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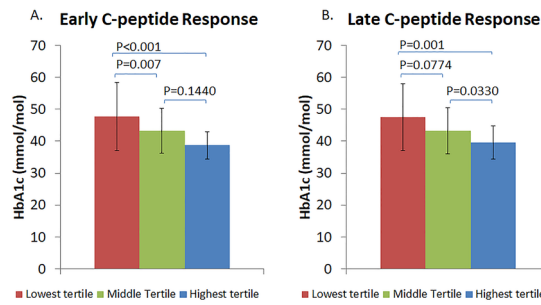
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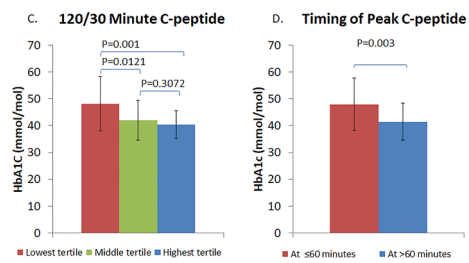
**Figure Legends**

**Figure 1: A. Comparison of HbA1c values (mean±SD) among the lowest, middle and highest tertiles of the early C-peptide response. B. Comparison of HbA1c values (mean±SD) among the lowest, middle and highest tertiles of the late C-peptide response. C. Comparison of HbA1c values (mean±SD) among the lowest, middle and highest tertiles of the 120/30 Minute C-peptide. D. Comparison of HbA1c values (mean±SD) among the peak C-peptide occurring at d60minutes and the peak C-peptide occurring at >60 minutes.**

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**Table 1: Metabolic characteristics of patients at the time of diagnosis:**

<b>Variable*</b>	<b>Value (N = 85)</b>
<b>A1C at diagnosis (mmol/mol)</b>	<b>43.54±8.46 (6.1±0.8%)</b>
<b>AUC C-peptide (ng/ml)</b>	<b>2.9±1.6 (1.0±0.5)**</b>
<b>Peak C-peptide (ng/ml)</b>	<b>3.8±2.3 (1.3±0.8)**</b>
<b>Early C-peptide Response (ng/ml)</b>	<b>1.4±1.1 (0.5±0.4)**</b>
<b>Late C-peptide Response (ng/ml)</b>	<b>1.9±3.0 (0.6±1.0)**</b>
<b>120/30 C-peptide Response</b>	<b>1.3±0.5</b>
<b>% Peak C-peptide at &gt;60 minutes</b>	<b>68</b>
<b>0 min C-peptide (ng/ml)</b>	<b>1.3±0.9 (0.4±0.3)**</b>
<b>30 min C-peptide (ng/ml)</b>	<b>2.7±1.5 (0.9±0.5)**</b>
<b>60 min C-peptide (ng/ml)</b>	<b>3.0±1.7 (1.0±0.6)**</b>

<b>90 min C-peptide (ng/ml)</b>	<b>3.4±2.0 (1.1±0.7)**</b>
<b>120 min C-peptide (ng/ml)</b>	<b>3.5±2.3 (1.2±0.8)**</b>

**\*Values are mean (±SD) unless otherwise indicated.**

**\*\* C-peptide Values in parenthesis are reported in SI units (nmol/L).**

**Table 2: Correlation coefficients and R<sup>2</sup> for associations of HbA1c with C-peptide indices at diagnosis.**

	<b>Correlation</b>	<b>R<sup>2</sup></b>	<b>P-value</b>
<b>AUC C-peptide</b>	<b>r=-0.34</b>	<b>11.6 %</b>	<b>&lt;0.001</b>
<b>Peak C-peptide</b>	<b>r=-0.37</b>	<b>13.7 %</b>	<b>&lt;0.001</b>
<b>Early C-peptide Response</b>	<b>r=-0.34</b>	<b>11.6 %</b>	<b>&lt;0.001</b>
<b>Late C-peptide Response</b>	<b>r=-0.38</b>	<b>14.4 %</b>	<b>&lt;0.001</b>
<b>120/30 C-peptide</b>	<b>r=-0.40</b>	<b>16.0 %</b>	<b>&lt;0.001</b>

**Table 3: R<sup>2</sup> values for associations of HbA1c with C-peptide indices in multivariable models**

Model	Unadjusted			BMI z-score and Age Included in Model		
	Overall R <sup>2</sup> of Model	Partial R <sup>2</sup>	P-Value for Partial R <sup>2</sup>	Overall R <sup>2</sup>	Partial R <sup>2</sup>	P-Value for Partial R <sup>2</sup>
<b>A) AUC C-peptide</b>	0.20	0.07	0.012	0.22	0.12	0.001
<b>120/30 min C-peptide</b>		0.12*	0.002		0.10*	0.004
<b>B) Peak C-peptide</b>	0.20	0.10	0.003	0.21	0.14	<0.001
<b>Peak C-peptide after 60 min</b>		0.10*	0.004		0.08*	0.013
<b>C) Early C-peptide</b>	0.25	0.14	<0.001	0.24	0.14	<0.001
<b>120/30 min C-peptide</b>		0.18**	<0.001		0.17**	<0.001
<b>D) Early C-peptide</b>	0.20	0.09	0.005	0.20	0.10	0.004

<b>Late C-peptide</b>		0.12**	0.001		0.13**	0.001
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\* $p \leq 0.01$ ; \*\* $p \leq 0.001$  for contribution to the  $R^2$  from the addition of the 2<sup>nd</sup> term in each model