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Predictive Value of C-Peptide Measures for Clinical Outcomes of β-Cell Replacement Therapy in Type 1 Diabetes: Report From the Collaborative Islet Transplant Registry (CITR)

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Optimal Cut Points for Predictors by Outcome	Absence of SHEs	HbA1c < 7.0%	HbA1c ≤ 6.5%	HbA1c < 7.0% & Absence of SHEs	HbA1c ≤ 6.5% & Absence of SHEs	Insulin Independence	Absence of SHEs, HbA1c ≤ 6.5%, & Insulin Independence
Fasting C-peptide (nmol/L)	0.070	0.150	0.310	0.140	0.310	0.260	0.330
Fasting CPGR (nmol/mmol)	0.023	0.054	0.054	0.044	0.045	0.044	0.054
MMTT-Stimulated C-peptide (nmol/L)	0.120	0.800	0.800	0.800	0.800	0.970	0.970
MMTT-Stimulated CPGR (nmol/mmol)	0.010	0.071	0.081	0.071	0.081	0.130	0.120

Optimal cut points for predictors by outcome (single randomly chosen observation per islet transplant recipient). CPGR, C-peptide-to-glucose ratio; MMTT, mixed-meal tolerance test; SHE, severe hypoglycemic episode.

ARTICLE HIGHLIGHTS

- C-peptide measures from 677 islet transplant recipients registered in the Clinical Islet Transplant Registry were evaluated to identify associations with primary outcomes of islet transplant and determine their predictive ability.
- The mixed-meal tolerance test–stimulated C-peptide-to-glucose ratio outperformed other measures in predictive ability for all primary outcomes except absence of severe hypoglycemic episodes, although it was only marginally better compared with a fasting C-peptide.
- Fasting C-peptide reliably predicts islet transplantation primary outcomes, and a value of ≥0.33 nmol/L is associated with optimal graft function.
- C-peptide targets should be considered as potential goals of β-cell replacement.

Predictive Value of C-Peptide Measures for Clinical Outcomes of β-Cell Replacement Therapy in Type 1 Diabetes: Report From the Collaborative Islet Transplant Registry (CITR)

David A. Baidal,[1] Cassandra M. Ballou,[2] Michael R. Rickels,[3] Thierry Berney,[4] Francois Pattou,[5] Elizabeth H. Payne,[2] Franca B. Barton,[2] and Rodolfo Alejandro,[1] for the CITR Investigators

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OBJECTIVE

To determine C-peptide measures and levels associated with positive glycemic control outcomes following islet transplant (ITx) in type 1 diabetes.

RESEARCH DESIGN AND METHODS

We evaluated Collaborative Islet Transplant Registry (CITR) islet-alone recipients with pretransplant C-peptide <0.1 nmol/L and mean follow-up of 4.6 ± 1.1 years (*n* = 677). Receiver operating characteristic area under the curve (ROC-AUC) was used to evaluate the predictive value of fasting and stimulated glucose and C-peptide measures for seven primary outcomes: *1*) absence of severe hypoglycemic events (ASHEs); *2*) HbA_{1c} <7.0%; *3*) HbA_{1c} <7.0% and ASHEs; *4*) HbA_{1c} ≤6.5%; *5*) HbA_{1c} ≤6.5% and ASHEs; *6*) insulin independence; and *7*) ASHEs, HbA_{1c} ≤6.5%, and insulin independence (the optimal outcome). Measures with the highest ROC-AUC were selected for determination of optimal cut points.

RESULTS

Fasting C-peptide was highly predictive for ASHE (ROC-AUC 0.906; optimal cut point 0.070 nmol/L) and the optimal outcome (ROC-AUC 0.845; optimal cut point 0.33 nmol/L). Mixed-meal tolerance test (MMTT)–stimulated C-peptide-to-glucose ratio (CPGR) outperformed both fasting and stimulated C-peptide for all outcomes except ASHE. The optimal cut point for the optimal outcome was 0.12 nmol/mmol for MMTT-stimulated CPGR and 0.97 nmol/L for MMTT-stimulated C-peptide.

CONCLUSIONS

Fasting C-peptide reliably predicts ITx primary outcomes. MMTT-stimulated CPGR provides marginally better prediction for composite ITx outcomes, including insulin independence. In the absence of an MMTT, a fasting C-peptide ≥0.33 nmol/L is a reassuring measure of optimal islet graft function. C-peptide targets represent excellent and easily determinable means to predict glycemic control outcomes after ITx and should be considered as potential goals of β-cell replacement.

Type 1 diabetes (T1D) results from autoimmune destruction of the insulin-producing β-cells in the endocrine pancreatic islets of Langerhans. While the majority of patients

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with T1D lose most β-cell function over time, ultimately becoming C-peptide negative, many will maintain some endogenous insulin secretion, as estimated from levels of C-peptide, for many years (1,2). There exists strong evidence from the Diabetes Control and Complications Trial (DCCT) that the maintenance of low levels of endogenous insulin secretion in T1D is clinically important. In the DCCT, a 90-min mixed-meal–stimulated C-peptide >0.2 nmol/L was associated with a reduced incidence of retinopathy and nephropathy and a decreased prevalence of severe hypoglycemia; these clinical benefits were more pronounced in those receiving intensive insulin therapy (3,4). Conversely, DCCT participants who had undetectable C-peptide were at greatest risk for severe hypoglycemia, regardless of treatment intensity (5). Residual endogenous insulin production has been associated with glucagon secretion in response to insulin-induced hypoglycemia (6), and the protection from severe hypoglycemia observed in the DCCT is likely explained by the presence of residual islet β-cells maintaining the paracrine signal for islet α-cell glucagon secretion in response to declining blood glucose (7,8).

Islet transplant (ITx) for adult patients with long-standing, C-peptide–negative T1D can restore endogenous insulin secretion and enable the attainment of near-normal glycemic control without the unwanted consequence of severe hypoglycemia (9,10). However, the transplant of islets isolated from more than one donor pancreas is often required to achieve insulin independence, and even those initially free from insulin may have a low engrafted islet β-cell mass (11). A low engrafted islet β-cell mass likely explains the observation that the majority of islet recipients return to requiring some insulin therapy by 3 years following transplantation (12). Nevertheless, up to 90% of insulin-dependent islet recipients with persistent graft function continue to experience amelioration of severe hypoglycemia episodes (SHEs) at 4 years after transplant (12). This observed protection from severe hypoglycemia is likely related to the transplanted islet β-cells providing the paracrine signal for islet α-cell glucagon secretion in response to declining blood glucose levels (13). Current criteria for ITx in patients with T1D include being C-peptide negative, which often is defined as a 90-min mixed-meal–stimulated C-peptide <0.1 nmol/L and having either hypoglycemia unawareness complicated by SHEs or the presence of a kidney graft for the treatment of diabetic nephropathy (9,10). Consequently, the goals of ITx are either to ameliorate hypoglycemia or protect a kidney graft from hyperglycemia. The presence of a C-peptide level ≥0.1 nmol/L is used to indicate evidence of ITx graft function (14).

The Collaborative Islet Transplant Registry (CITR) has been established to monitor progress and safety of ITx by using data from the U.S., Canada, and several participating centers in Europe and Australia and represents the most comprehensive collection of information on clinical ITx performed over the past two decades. The CITR collects metabolic data, including fasting and stimulated glucose and C-peptide (following a mixed meal tolerance test [MMTT], oral glucose tolerance test [OGTT], intravenous glucose tolerance test [IVGTT], arginine stimulation test, or intravenous glucagon stimulation test) and HbA_{1c}. For our study, we evaluated how CITR C-peptide data relate to the primary glycemic control outcomes of ITx, first by determining the association between fasting and stimulated C-peptide with the primary glycemic control outcomes including absence of SHEs (ASHEs), HbA_{1c}, and insulin independence and then by investigating the predictive value of all the available concurrent C-peptide metabolic test summary measures on each of the primary outcomes. We hypothesized that *1*) the proportion of recipients achieving the primary outcomes will depend on each incremental increase in concurrent C-peptide level as an indicator of islet graft β-cell function, *2*) that a significant proportion of recipients will require a C-peptide ≥0.3 nmol/L to achieve insulin independence, and *3*) that protection from severe hypoglycemia will be apparent with a C-peptide ≥0.1 nmol/L (14). An additional hypothesis is that a greater proportion of those with a stimulated C-peptide >0.2 nmol/L will achieve glycemic control targets and be protected from severe hypoglycemia (4). This hypothesis was investigated systematically across all stimulated C-peptide measures, as well as other summary measures of metabolic testing.

RESEARCH DESIGN AND METHODS

ITx Recipients

Islet-alone transplant recipients who were C-peptide negative (<0.1 nmol/L) before transplant and enrolled in the CITR as of 14 August 2020 comprised the cohort for these analyses. A total of 677 of 985 islet-alone transplant recipients were C-peptide negative pretransplant and were included in this report.

Primary Outcomes of ITx

Primary outcomes of ITx were defined as follows: *1*) ASHEs; *2*) HbA_{1c} <7.0%; *3*) HbA_{1c} <7.0% and ASHEs; *4*) HbA_{1c} ≤6.5%; *5*) HbA_{1c} ≤6.5% and ASHEs; *6*) insulin independence; and *7*) ASHEs, HbA_{1c} ≤6.5%, and insulin independence. This last composite outcome was defined as the optimal outcome consistent with current consensus recommendations (15). To properly ascertain severe hypoglycemia, the protocol specifies that *1*) the definition of severe hypoglycemia require the assistance of another person to recover; *2*) ascertainment at every scheduled follow-up visit, whether in person or by telephone, as a self-reported outcome that the recipient had to log into their diary; and *3*) verification of the reported data versus the clinical record onsite visit, with missing data required to be captured. A recipient was deemed to be insulin independent if able to remain off exogenous insulin for at least 14 consecutive days while maintaining fasting blood glucose levels ≤140 mg/dL and >2-h postprandial blood glucose levels ≤180 mg/dL.

Metabolic Measures

Fasting and stimulated glucose and C-peptide measures were taken from any available metabolic test (arginine stimulation test, IVGTT, OGTT, glucagon stimulation test, and MMTT) at each visit.

Statistical Analysis

The CITR primary efficacy data are collected at protocol-designated time points through 10 years from last transplant, regardless of islet graft failure (C-peptide <0.1 nmol/L or undetectable for three consecutive visits without recovery or retransplant). In the event of complete graft failure and no data collected at the visit, the following data were imputed: Insulin use was set as using exogenous insulin, and C-peptide was set as 0.0 nmol/L. HbA_{1c} and SHEs were set to missing and analyzed as missing at random (outcome not related to absence of data). Approximately 76% of the cohort received more than one ITx. Primary efficacy outcomes were analyzed following

the last islet infusion to take into account all islet infusions given to each individual. The data coordinating center verified participant voluntary informed consent. In the North American sites, outcomes were verified by site visit throughout the duration of the registry.

Analyses used all of a recipient's primary outcome values available at each time point from the pretransplant visit and annually at 1–5 years after the last infusion, unless otherwise noted. The percentage of recipients with each primary outcome at each annual time point was compared across levels of the predictive (independent) variable.

At 1-year after the last infusion, 86% of recipients in the cohort analyzed (n = 677) had a fasting C-peptide reported, declining to 80% at 2 years, 73% at 3 years, 66% at 4 years, and 58% at 5 years after the last infusion. At 1-year after the last infusion, 44% of recipients in the cohort analyzed had stimulated C-peptide reported, declining to 33% at 2 years, 27% at 3 years, 21% at 4 years, and 17% at 5 years after the last infusion. The percentage of recipients who had a particular metabolic test at any time point was higher for the MMTT (22%) and was distributed as follows for the other tests: 16% for the arginine stimulation test, 11% for the IVGTT, 9% for the OGTT, and 9% for the glucagon stimulation test. A particular metabolic test was not specified for 8% of recipients. The remaining 25% had only fasting measures reported. At each time point, recipients were classified according to their concurrent fasting C-peptide level as follows: 0.0 to $<$0.1, 0.1 to $<$0.2, 0.2 to $<$0.3, and $\geq$0.3 nmol/L. This classification was used as the independent variable of the other primary outcomes at each of the follow-up annual time points. This analysis was further performed with recipients classified according to concurrent stimulated C-peptide level, as available from any of the stimulation tests as follows (0.0 to $<$0.2, 0.2 to $<$0.4, 0.4 to $<$0.8, and $\geq$0.8 nmol/L [regardless of concurrent fasting C-peptide]), which was then considered similarly as the predictor of the primary outcomes.

While ascertainment of C-peptide and the primary outcomes declined with increasing follow-up, and more often after loss of graft function, bias is reduced by imputing zero C-peptide and insulin dependence after graft loss. The reduction in the reporting of C-peptide with increased follow-up appears to be primarily related to a reduction in recipients' engagement with their transplant sites as graft function declined.

Predictive value was assessed by the receiver operating characteristic area under the curve ((ROC-AUC). An ROC-AUC of 0.5 indicated prediction of no better than chance alone; ROC-AUC of $>$0.90 was considered highly predictive, and $>$0.80 was considered significantly predictive. For these analyses, no other explanatory factors were included in order to isolate the predictive value of each concurrent metabolic measure alone. The same approach was used to assess the predictive value of each summary measure from metabolic testing, including various measures of C-peptide (i.e., fasting, stimulated, and AUC), and these measures were compared for each outcome. To account for the influence of the prevailing glucose concentration on C-peptide levels, we also evaluated the fasting, stimulated, and AUC C-peptide-to-glucose ratio (CPGR) (16). Comparisons between measures of C-peptide were conducted on the subset of recipients who had available data for all measures being compared (i.e., fasting C-peptide, stimulated C-peptide, fasting CPGR, and stimulated CPGR in Fig. 3). For this reason, ROC-AUC values shown for comparisons may differ slightly from the values shown in Supplementary Table 2, which includes all available data for each measure alone.

The Youden index, which takes into account sensitivity and specificity measures, was used to further examine the optimal cut points for each predictor by outcome. Optimal cut points for predicting primary outcomes were examined by outcome for fasting and stimulated C-peptide, as well as other metabolic testing summary measures. A single observation from each islet-alone recipient chosen at random was used for this analysis.

The predictive value of the concurrent C-peptide level was assessed with generalized estimating equations, using repeated measures for each recipient and including follow-up time in the regression models to account for the known decline of primary outcome success rates over time. In this observational study with no formal a priori experiment-wise type I error structure and multiple statistical testing, $P < 0.001$ was considered unlikely to occur by chance alone, and $P < 0.01$ was considered suggestive of a noteworthy association.

RESULTS

Recipients were mean ± SD 46 ± 11 years of age, had diabetes for 29 ± 11 years and a BMI of 23.8 ± 2.9 kg/m^2, used 0.55 ± 0.18 units/kg per day of insulin, and had a mean HbA_{1c} of 7.9 ± 1.3% pretransplant. Recipients received a mean of 852,000 ± 419,000 total islet equivalents over 2.1 ± 0.7 islet infusions and had 4.6 ± 1.1 years of follow-up after their last islet infusion. Sixty-one percent of recipients were female, and 77% experienced SHEs in the year before their first transplant. Other notable donor and islet characteristics are summarized in Supplementary Table 1.

Fasting and Stimulated C-Peptide and Prevalence of Each Primary Outcome

We first evaluated the relationship between the fasting and stimulated C-peptide level at each annual time point after the last infusion and the prevalence of each of the primary outcomes (Figs. 1 and 2). The prevalence rate of primary outcomes throughout follow-up was significantly higher, with increasing levels of both concurrent fasting and stimulated C-peptide ($P < 0.001$ for every outcome). These rates are adjusted for no other factors. Notably, there is no decay over 5 years in the predictive value of C-peptide for any of the primary outcomes, even though there is decay over those 5 years in the primary outcomes themselves. To clarify, these are not cohorts; rather, a particular recipient appears in each panel of the display only on the basis of only their C-peptide level at that time, and a recipient can move from one predictive level group to another between years.

Higher levels of concurrent C-peptide are associated with higher levels of insulin independence ($P < 0.0001$). If fasting C-peptide levels can be maintained at $\geq$0.3 nmol/L, insulin independence reliably persists at the 70% level. Within each C-peptide level, there was no decay of insulin independence rates with increasing years of follow-up; only the concurrent C-peptide level determined the probability of insulin independence. The number of recipients who remained

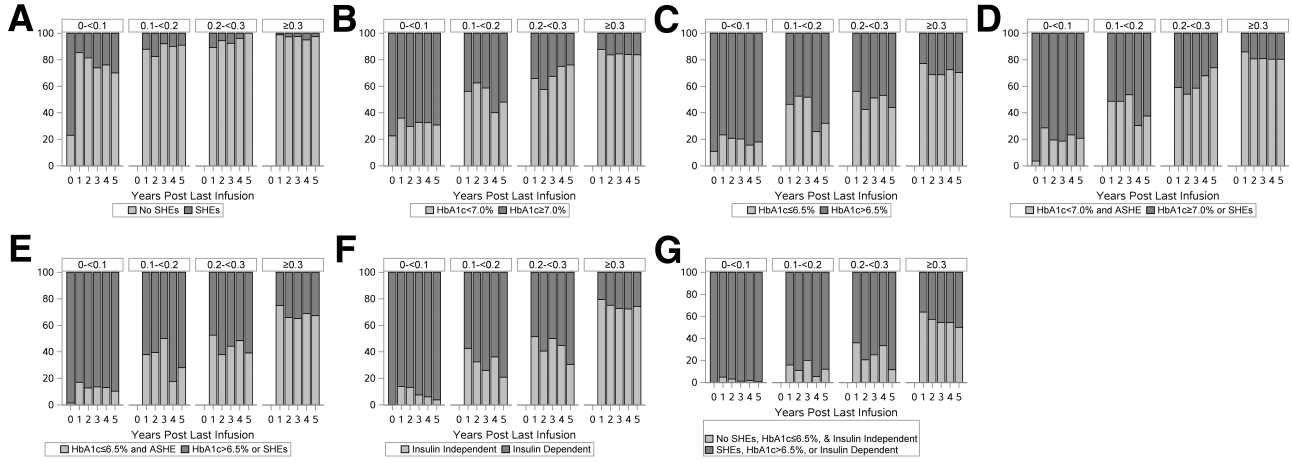

Figure 1—Predictive value of concurrent fasting C-peptide ranges/thresholds (nmol/L) on outcomes of clinical ITx. *A*: ASHEs. *B*: HbA_{1c} <7.0%. *C*: HbA_{1c} ≤6.5%. *D*: HbA_{1c} <7.0% and ASHEs. *E*: HbA_{1c} ≤6.5% and ASHEs. *F*: Insulin independence. *G*: ASHEs, HbA_{1c} ≤6.5%, and insulin independence.

at their C-peptide level over the 5 years of follow-up declined, while the number of graft function losses (C-peptide <0.1 nmol/L) increased over follow-up (see the *N* rows of Supplementary Table 3). Results are consistent for stimulated C-peptide levels ≥0.8 nmol/L (Supplementary Table 4).

For ASHEs, any level of C-peptide at any time point after ITx conferred very high probability of resolving SHE throughout follow-up. Any positive fasting C-peptide (≥0.1 nmol/L) virtually eliminated SHEs; the slightly increasing probability of ASHEs with increasing levels of C-peptide was statistically significant for all fasting C-peptide levels (odds ratio [OR] 1.13 [95% CI 1.03–1.24] for fasting C-peptide of 0.1 to <0.2 nmol/L relative to C-peptide <0.1 nmol/L; OR 1.20 [95% CI 1.10–1.31] for C-peptide of 0.2 to <0.3 nmol/L; OR 1.24 [95% CI 1.15–1.34] for C-peptide ≥0.3 nmol/L) (Fig. 1). Results are generally consistent for stimulated C-peptide levels (OR 1.11 [95% CI 0.96–1.27] for stimulated C-peptide of 0.2 to <0.4 nmol/L relative to C-peptide <0.2 nmol/L; OR 1.17 [95% CI 1.05–1.30] for C-peptide of 0.4 to <0.8 nmol/L; OR 1.20 [95% CI 1.08–1.33] for C-peptide ≥0.8 nmol/L) (Supplementary Table 4).

HbA_{1c} <7.0% is also largely driven by concurrent C-peptide level, with rates of 80–90% sustained throughout 5 years in those with fasting C-peptide ≥0.3 nmol/L or stimulated C-peptide >0.8 nmol/L and 40–80% for those with fasting C-peptide of 0.1 to <0.3 nmol/L or stimulated C-peptide of 0.2 to <0.4 nmol/L (P < 0.0001 and ORs with 95% CIs well above 1.0 relative to fasting C-peptide <0.1 nmol/L or stimulated C-peptide <0.2 nmol/L, respectively).

For HbA_{1c} ≤6.5%, rates of 70–80% were observed throughout 5 years in those with fasting C-peptide ≥0.3 nmol/L or stimulated C-peptide ≥0.8 nmol/L, 20–60% for those with fasting C-peptide of 0.1 to <0.3 nmol/L, and 30–80% for those with stimulated C-peptide of 0.2 of <0.8 nmol/L (P < 0.0001 and ORs with 95% CIs well above 1.0 relative to fasting C-peptide <0.1 nmol/L or stimulated C-peptide <0.2 nmol/L, respectively).

For the optimal outcome comprising the composite of ASHEs, HbA_{1c} ≤6.5%, and insulin independence, lower rates were observed compared with other outcomes, even in patients included in the highest fasting and C-peptide categories. Rates of 50% throughout year 5 were observed in patients with fasting C-peptide ≥0.3 nmol/L and 60% in those with stimulated C-peptide ≥0.8 nmol/L.

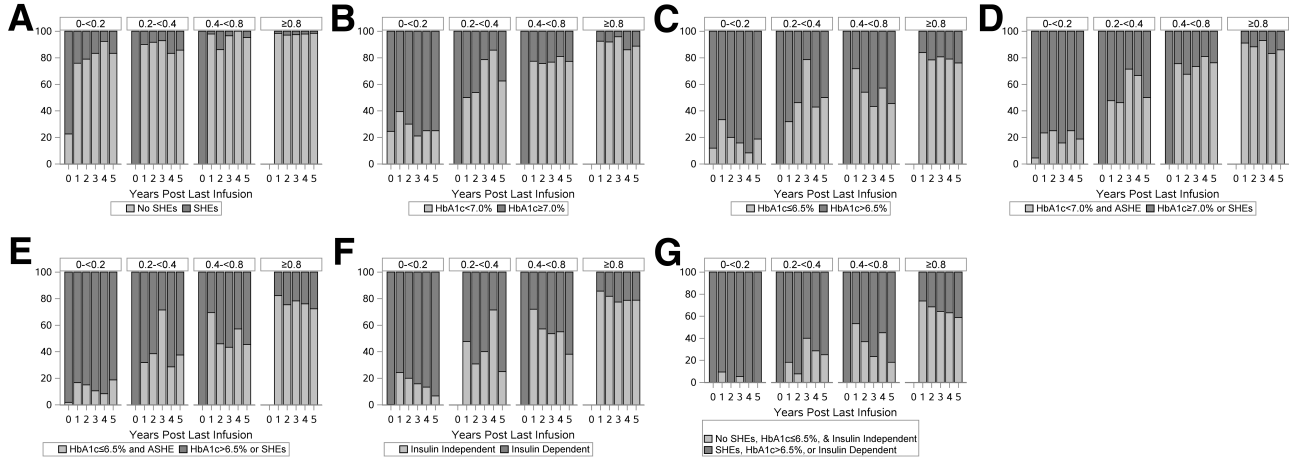

Figure 2—Predictive value of concurrent stimulated C-peptide on outcomes of clinical ITx. *A*: ASHEs. *B*: HbA_{1c} <7.0%. *C*: HbA_{1c} ≤6.5%. *D*: HbA_{1c} <7.0% and ASHEs. *E*: HbA_{1c} ≤6.5% and ASHEs. *F*: Insulin independence. *G*: ASHEs, HbA_{1c} ≤6.5%, and insulin independence.

Predictive Value of C-Peptide Measures for Primary Outcomes

We then selected fasting and stimulated C-peptide measures to identify optimal cut points for predictors by outcome of ITx. Fasting measures comprised the fasting C-peptide (which included any fasting C-peptide obtained at the start of the various stimulation tests performed) and the fasting CPGR. For stimulated C-peptide measures, the predictive value of all tested measures from the various metabolic tests was comparable for the primary outcomes (data not shown), with the exception of the MMTT-stimulated CPGR, which was superior to the OGTT-stimulated C-peptide for insulin independence and the optimal outcome (Supplementary Fig. 1). In view of this finding, we selected the stimulated measures from the MMTT (stimulated C-peptide and CPGR), as MMTT is a noninvasive test that is currently more widely performed for assessment of β-cell function following ITx and provides robust C-peptide stimulation by means of the incretin effect.

Fasting C-peptide alone was highly predictive for all outcomes, with the highest ROC-AUC for ASHEs (0.906; $P < 0.0001$) and the lowest for HbA_{1c} ≤6.5% and ASHEs (0.702; $P < 0.0001$) (Supplementary Table 2). However, the fasting CPGR had superior predictive ability to fasting C-peptide alone for all primary outcomes except ASHEs (Supplementary Fig. 2). Notably, the MMTT-stimulated CPGR outperformed, although only marginally, all the other measures but for the ASHE outcome, where all predictive measures performed similarly (Fig. 3).

Optimal cut point analyses showed that a fasting C-peptide of 0.07 nmol/L was predictive of ASHEs (Table 1). However, substantially higher levels were required to achieve recommended glycemic targets. Indeed, a level of 0.31 nmol/L (fourfold higher) was required for the composite outcome of HbA_{1c} ≤6.5% and ASHEs. For insulin independence, the cut point value was 0.26 nmol/L, and to achieve the optimal outcome of ASHEs, HbA_{1c} ≤6.5%, and insulin independence, a fasting C-peptide of 0.33 nmol/L was required.

For MMTT-stimulated C-peptide, a level of 0.12 nmol/L predicted ASHEs (Table 1). Similar to the fasting C-peptide, higher levels were required for improved glycemic control. A value of 0.80 nmol/L was predictive of HbA_{1c} ≤6.5% and ASHEs, whereas a value of 0.97 nmol/L was associated with both insulin independence and the optimal outcome. A fasting CPGR of 0.02 nmol/mmol was sufficient for ASHEs, and values between 0.04 and 0.05 nmol/mmol were predictive of all other primary outcomes. Finally, an MMTT-stimulated CPGR value of 0.01 nmol/mmol resulted in ASHEs, values between 0.07 and 0.08 nmol/mmol predicted excellent metabolic control in combination with ASHEs, and values between 0.12 and 0.13 nmol/mmol resulted in insulin independence and the optimal outcome.

CONCLUSIONS

These results show that C-peptide levels reliably predict rates of primary outcomes of clinical ITx, and the higher the C-peptide level, the greater the likelihood of achieving each outcome. Notably, a fasting C-peptide ≥0.3 nmol/L was associated with 70% insulin independence rates, and these results were maintained regardless of years after infusion. Achievement of glycemic control, assessed by an HbA_{1c} <7.0%, was also highly predicted by concurrent C-peptide level, again regardless of years after infusion, with expected 80–90% rates of excellent HbA_{1c} outcomes when fasting C-peptide levels are ≥0.3 nmol/L. Most importantly is the fact that SHEs, which are associated with increased mortality risk, are virtually eliminated with ITx, regardless of the level of restored C-peptide. However, restoration of C-peptide may not be the only factor accounting for the improvement in rates of SHEs, as education and diabetes self-management are well known to contribute to SHE avoidance in patients treated

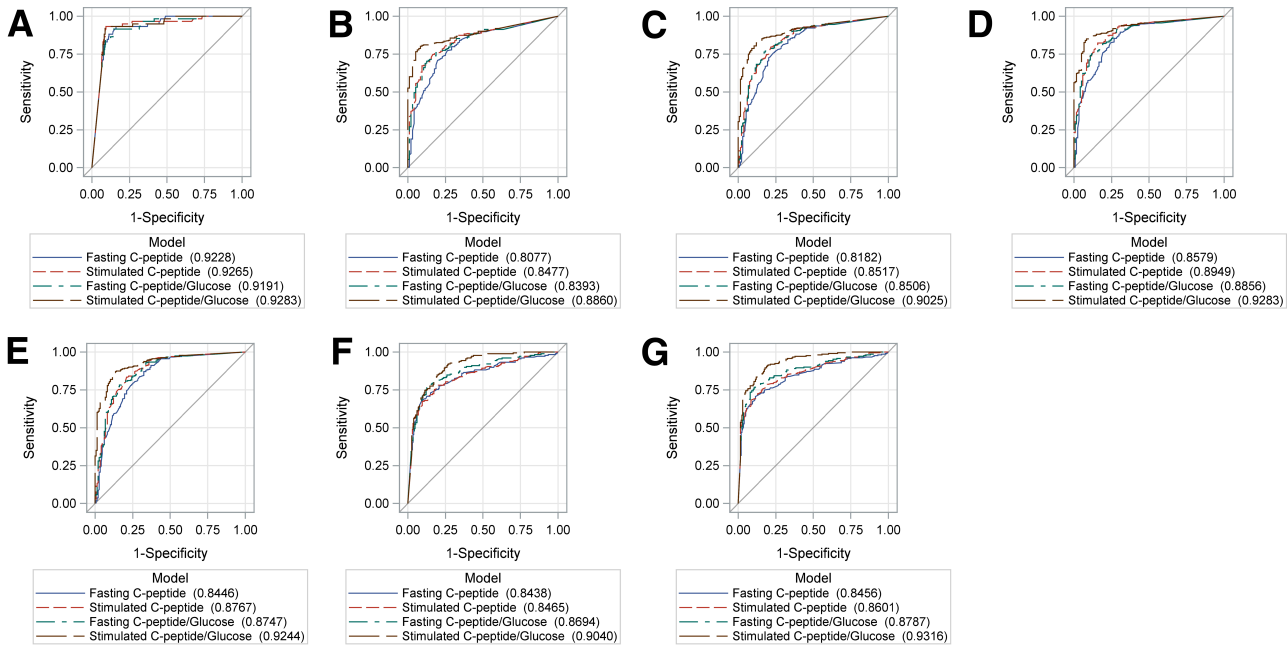

Figure 3—Comparison of predictive value (ROC-AUC) of fasting C-peptide vs. other predictors for each primary outcome of clinical ITx. *A*: ASHEs (*P* ns). *B*: HbA_{1c} <7.0% ($P < 0.0001$). *C*: HbA_{1c} ≤6.5% ($P < 0.0001$). *D*: HbA_{1c} <7.0% and ASHEs ($P < 0.0001$). *E*: HbA_{1c} ≤6.5% and ASHEs ($P < 0.0001$). *F*: Insulin independence ($P < 0.0001$). *G*: ASHEs, HbA_{1c} ≤6.5%, and insulin independence ($P < 0.0001$).

Table 1—Optimal cut points for predictors by outcome (single randomly chosen observation per ITx recipient)

	ASHEs	HbA_{1c} <7.0%	HbA_{1c} ≤6.5%	HbA_{1c} <7.0% and ASHEs	HbA_{1c} ≤6.5% and ASHEs	Insulin independence	ASHEs, HbA_{1c} ≤6.5%, and insulin independence
Fasting C-peptide (nmol/L)	0.07	0.15	0.31	0.14	0.31	0.26	0.33
Fasting CPGR (nmol/mmol)	0.023	0.054	0.054	0.044	0.045	0.044	0.054
MMTT-stimulated C-peptide (nmol/L)	0.12	0.80	0.80	0.80	0.80	0.97	0.97
MMTT-stimulated CPGR (nmol/mmol)	0.010	0.071	0.081	0.071	0.081	0.13	0.12

with insulin. Also important to note is that, although the selection of immunosuppressive strategy impacts the ability to sustain the C-peptide level (data not shown), C-peptide's predictive value of good clinical outcomes of ITx holds regardless of how it is achieved and maintained.

While other summary measures from MMTT can improve slightly on the predictive value of fasting C-peptide alone, our data suggest that a fasting C-peptide can be used to reliably monitor islet graft function, as has been previously reported with consideration of the fasting glucose (16,17) and are now shown as well to predict clinical outcomes.

Our findings are in line with literature demonstrating that even minute residual endogenous insulin production can protect against severe hypoglycemia (7,18). However, higher C-peptide levels are required for achievement of optimal metabolic control (6). This is also supported by the β-score (a composite measure of β-cell function following ITx), where excellent graft function is defined by the maximal score of 8 but a score of only >3, associated with partial graft function, is sufficient to eliminate hypoglycemia (14). In the DCCT, patients with T1D with a stimulated C-peptide >0.2 nmol/L had better outcomes related to glycemic control, frequency of hypoglycemia, and microvascular complications compared with those with a lower C-peptide (4), although demonstration of glucose-responsive islet β- and α-cell function that relate to improved glycemic control may be more easily appreciated with stimulated C-peptide >0.4 nmol/L (6).

In adult patients with T1D and residual C-peptide, stimulated C-peptide values >0.4 nmol/L were associated with 70% time spent in glucose range 70–180 mg/dL (6). Similarly, in a U.K. cohort of ITx recipients, those with a stimulated C-peptide >0.5 nmol/L achieved 75% time spent in glucose range 54–180 mg/dL, while those with stimulated C-peptide values >1.0 nmol/L were able to achieve almost 100% time spent in glucose range 54–180 mg/dL (19). In the phase 3 Clinical Islet Transplantation (CIT-07) trial, a mean fasting C-peptide level of 0.49 nmol/L with a concurrent mean stimulated C-peptide value of 1.39 nmol/L obtained 1 year following the first islet infusion were associated with a 52.5% insulin independence rate, an average HbA_{1c} of 5.6%, and 84.9% time in glucose range 54–180 mg/dL (9). These data highlight the importance of C-peptide levels on glycemic control outcomes. However, the optimal C-peptide thresholds at which clinically important glycemic control outcomes are met have not been established.

Our study has several limitations. First, there was no standardization regarding the metabolic tests used for assessing stimulated C-peptide. Each participating site used the metabolic tests specific to their clinical ITx protocol. Therefore, transplant recipients were not assigned to receive a particular metabolic test at a particular time point, which may have led to site-specific effects or other differences between groups of recipients (e.g., either who received any test vs. no test or who received test X vs. test Y) impacting the results. Second, reporting of C-peptide by participating sites declined with increasing follow-up. This decline appears to have been primarily related to a reduction in recipients' engagement with their transplant site as graft function declined. While ascertainment of C-peptide and the primary outcomes declined with increasing follow-up, and more often after loss of graft function, bias is reduced by imputing zero C-peptide and insulin dependence after graft loss. However, no imputations were made for HbA_{1c} and SHEs. Third, increased glucose monitoring after transplant may have on its own reduced the rate of severe hypoglycemia. In the pretransplant period, recipients monitored their blood glucose per standard of care with close follow-up by their endocrinologists. Following transplant, recipients were required to monitor blood glucose levels at a minimum of four times a day (before meals and bedtime), and data were collected at every scheduled CITR follow-up visit. Although it is possible that more frequent monitoring of blood glucose and frequent communication with the transplant team may have led to optimization of insulin management and reduction in severe hypoglycemia after transplant, this was not specifically evaluated in the registry, and there is not sufficient pretransplant data to perform such an analysis.

On the other hand, strengths of our analyses include the large registry data set available and the identification of optimal C-peptide cut points for clinically important outcomes. Indeed, we show that a fasting C-peptide value of ≥0.33 nmol/L is highly predictive for the optimal outcome following ITx. This is of particular importance to the field as this simple and low-cost measure can be easily obtained from a fasting sample prior to or during clinical visits, providing critical information regarding functional graft status and metabolic control.

Therefore, the focus of clinical management should be to maximize retention of C-peptide function in the graft, namely by implementing the most favorable factors for maximizing C-peptide level through use of evidence-based optimal immunosuppression strategies and peritransplant management that support engraftment of an adequate islet mass (20). Several β-cell replacement strategies continue to evolve and are currently under evaluation in small clinical trials, with

outcomes centered on metabolic control and C-peptide positivity (21). However, it may be time to raise the bar and consider specific fasting and stimulated C-peptide targets as potential outcomes to ensure success of these therapies positively impacting the lives of patients with T1D complicated by problematic hypoglycemia (22).

In conclusion, fasting C-peptide reliably predicted rates of ITx primary outcomes and was similar to other C-peptide measures at predicting ASHEs. Even marginal fasting C-peptide (≥0.07 nmol) was sufficient to largely eliminate SHEs; however, higher levels are required to achieve optimal ITx outcomes. While MMTT-stimulated C-peptide measures can improve slightly on the predictive value of fasting C-peptide alone, fasting C-peptide still provided robust prediction. In the absence of an MMTT, a fasting C-peptide ≥0.33 nmol/L (≥0.99 ng/mL) is a reassuring measure, as it is associated with optimal metabolic control in ITx recipients. C-peptide targets represent excellent, commonly used, and easily determinable means to predict glycemic control outcomes after ITx and should be considered as potential goals of β-cell replacement strategies.

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