



Demonstration of an Intrinsic Relationship Between Endogenous C-Peptide Concentration and Determinants of Glycemic Control in Type 1 Diabetes Following Islet Transplantation

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OBJECTIVE

Maintenance of endogenous pancreatic β -cell function could be an important goal in the management of type 1 diabetes. However, the impact of stimulated C-peptide level on overall glycemic control is unknown. The relationship between C-peptide and parameters of glucose control was therefore characterized in a cohort with rapidly changing β -cell function following islet transplantation.

RESEARCH DESIGN AND METHODS

Standardized mixed-meal tolerance test was undertaken in 12 consecutive islet recipients at 1–6-month intervals, with graft function determined by 90-min stimulated C-peptide. Continuous glucose monitoring was undertaken in the week preceding each assessment and the relationship between C-peptide and glucose control evaluated by mixed Poisson regression.

RESULTS

Recipients completed 5 (1–14) [median (range)] clinical assessments over 18 (1–51) months posttransplant encompassing a wide range of stimulated C-peptide levels (7–2,622 pmol/L). Increasing β -cell function across predefined C-peptide groups was associated with reduced insulin dose, HbA_{1c}, mean glucose (low [<200 pmol/L] 10.7 vs. excellent [$>1,000$ pmol/L] 7.5 mmol/L), and glucose SD (low, 4.4 vs. excellent, 1.4 mmol/L). Highly statistically significant continuous associations between stimulated C-peptide and mean interstitial glucose (lower by 2.5% [95% CI 1.5–3.5%] per 100 pmol/L higher C-peptide), glucose SD, time outside glucose target range, and measures of hyper-/hypoglycemia risk were confirmed.

CONCLUSIONS

Repeated assessment of islet transplant recipients has enabled modeling of the relationship between endogenous β -cell function and measures of glycemic control providing quantitative estimates of likely impact of an acute change in β -cell function in individuals with type 1 diabetes.

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Type 1 diabetes has conventionally been considered a disease characterized by inexorable progression to absolute insulin deficiency. Recent data have challenged this paradigm, showing evidence of C-peptide microsecretion in the majority of individuals with long-standing type 1 diabetes (1–3). The ultimate goal of disease-modifying interventions for diabetes is cure defined by restoration of normoglycemia and insulin independence. Increasingly, a secondary goal of maintaining or restoring C-peptide positivity [typically measured stimulated within a meal tolerance test (4)] is being proposed in trials of immunomodulation early in the course of type 1 diabetes (5) and β -cell replacement therapy in those with long-standing C-peptide negative disease (6). This is justified by evidence from the Diabetes Control and Complications Trial (DCCT) that modest concentrations of C-peptide at study entry were associated with reduced microvascular complications over the next 6.5 years and reduced severe hypoglycemia (7,8). A recent reanalysis has demonstrated a continuous relationship between C-peptide concentration at trial commencement and subsequent insulin dose, HbA_{1c}, and retinopathy (9). The implication is that an increase in endogenous β -cell function facilitates improved glycemic control, leading to reduction in microvascular complications.

In the setting of islet transplantation, continuous glucose monitoring (CGM) has been used to demonstrate improved blood glucose control in patients with functioning grafts (10–15). However, the continuous association between graft function measured by stimulated C-peptide and impact on day-to-day glycemic control within an individual has not been studied. We aimed to characterize the relationship between stimulated C-peptide and parameters of glucose control determined by CGM profile in a cohort with rapidly changing C-peptide levels following islet transplantation.

RESEARCH DESIGN AND METHODS

Following ethical approval and informed written consent, all recipients of an islet transplant within the U.K. nationally funded program at Newcastle Upon Tyne Hospitals NHS Foundation Trust between October 2008 and December 2012 agreed to take part in this prospective

cohort study. Criteria for transplantation included C-peptide–negative type 1 diabetes without insulin resistance, complicated by recurrent severe hypoglycemia (16). Details of listing criteria, protocols for islet procurement, assessment, transport, and transplantation, together with immunosuppression and peri-transplant management, have been previously reported (6,17,18).

Formal metabolic evaluation including hypoglycemia awareness assessment (by Clarke and Gold questionnaires [score ≥ 4 , impaired awareness of hypoglycemia]) (6), record of severe hypoglycemic episodes requiring assistance in treatment over the preceding 12 months, total daily insulin dose, weight, and HbA_{1c} (TOSOH G7/G8 analyzer, with National Glycohemoglobin Standardization Program [DCCT] standardization until June 2009 and transition to International Federation of Clinical Chemistry and Laboratory Medicine standardization thereafter) was undertaken pretransplant. Participants were reassessed at 1, 3, 6, and 12 months posttransplant and 3–6 months thereafter.

Standardized mixed-meal tolerance test (MTT) (4) including 0- and 90-min serum C-peptide (PerkinElmer AutoDELFIA until December 2011; Siemens IMMULITE 2000, Siemens, Erlangen, Germany after December 2011; equivalence confirmed including excellent correlation [Pearson $R^2 = 0.98$]) was undertaken at all post-transplant assessments. Participants attended fasted and, if on exogenous insulin therapy, were advised to withhold their prebreakfast short-acting insulin dose on the day of assessment, with all tests organized to commence at 9 A.M. Insulin independence was defined as cessation of insulin for >14 days, with the decision to stop insulin therapy post-transplantation made following review of blood glucose levels by the clinical team (19).

In the week preceding each post-transplant metabolic assessment, a CGM sensor (iPro1; Medtronic, Minneapolis, MN) was sited on the anterior abdominal wall by trained and experienced members of the research team. The system registers glucose concentration every 10 s and stores an average value every 5 min, within a range of 2.2–22.2 mmol/L (40–400 mg/dL). Participants were blinded to CGM data but were provided with a OneTouch

blood glucose meter (LifeScan, High Wycombe, U.K.) with standardized instructions on checking blood glucose at least once every 12 h to enable standardized CGM calibration. A 3–5-day continuous blood glucose monitoring record was obtained in each participant at each time point, with device removal prior to MTT.

Data from the sensor and calibration blood glucose meter were uploaded using Solutions software (Medtronic). Records in which mean absolute difference between sensor glucose and capillary blood glucose readings exceeded 28% over a 24-h period of CGM and periods in which the sensor failed to record blood glucose values were excluded from analysis.

In total, 7,211 h of CGM data were analyzed from 74 CGM records. Duration of normoglycemia (3.0–10.0 mmol/L), hypoglycemia (<3.0 mmol/L), and hyperglycemia (>10.0 mmol/L) were calculated and expressed as percentages of total analyzed CGM data from each recording.

Measures of blood glucose variability and estimates of hypo- and hyperglycemia risk [SD of blood glucose; average daily risk ratio (ADRR) (20), low blood glucose index (LBGI), and high blood glucose index (HBGI) (21)] were calculated by analyzing CGM data within the EasyGV program (www.easygv.co.uk) (22). These risk indices have been designed to overcome the greater influence of hyperglycemic as opposed to hypoglycemic excursions on measures of glucose variability such as SD, given the skewed distribution of the data around the mean. LBGI and HBGI are derived from a nonlinear transformation of the blood glucose scale, creating a symmetrical distribution of low and high glucose values. LBGI increases as frequency and extent of biochemical hypoglycemia increases, and it has been used to predict future severe hypoglycemia (23). Similarly, the HBGI is designed specifically to assess hyperglycemia risk (24). The sum of LBGI and HBGI provides a nonnegative number from 0–100 with moderate risk empirically defined as LBGI 2.5–5.0 and HBGI 4.5–9.0 (25). The ADRR (20) again takes into account the asymmetric nature of the blood glucose scale, predicting the risk of combined low and high glucose variability.

Statistical Analysis

Relationships among stimulated C-peptide, metabolic status, and CGM glucose profile were explored by analysis of all posttransplant assessments. β -Cell function (90-min MTT C-peptide) was categorized into four a priori agreed groups: low function C-peptide, <200 pmol/L [the original cutoff of significant endogenous insulin defined by DCCT (26)]; moderate function, 200–500 pmol/L; good function, 500–1,000 pmol/L; and excellent function, >1,000 pmol/L.

Results are reported as median (minimum to maximum range) or median [interquartile range]. The relationship between C-peptide and blood glucose control was investigated using a mixed Poisson regression model (Stata 12 data analysis and statistical software). The dependent variable in each analysis was the measure of blood glucose control, either fitted directly or after an appropriate transformation. Variation between participants and variation between observations within participants were included as random effects; C-peptide was included as a fixed effect. These models were used to generate plots of predicted values of the indicator against a range of C-peptide values.

Proportion of time spent within target near-normoglycemic range (3.0–10.0 mmol/L) was modeled by considering the proportion of time spent outside this range. The dependent variable was the number of 5-min blocks of time in which blood glucose levels were either <3.0 or >10.0 mmol/L. A Poisson error structure was assumed for the variation between observations within patients; variation between subjects was assumed to follow a γ distribution. The total number of blocks observed during a particular observation interval was included as an exposure variable (\log_e [total number of blocks] included as a covariate with the regression coefficient constrained to 1).

Plots of mean plasma-calibrated interstitial glucose and blood glucose variability against C-peptide suggested a nonlinear relationship between the two variables: both blood glucose and SD cannot be less than zero, and therefore, a linear relationship was not plausible. Taking a log transformation resulted in a plausible model and plots that were consistent with a linear trend

on the log scale. For the log-transformed observations, normal distributions were assumed for both variation between participants and variation between observations within participants.

The analyses of average daily risk ratio, HbG1, and LBG1 were based on log-transformed values. For the LBG1, 1 was added to all values prior to log transformation.

RESULTS

Impact of Islet Transplantation on Endogenous C-Peptide and Metabolic Parameters

Twelve consecutive islet transplant recipients agreed to participate (Table 1). Participants received a total of 20 islet transplants (single graft: $n = 5$; two grafts: $n = 6$; and three grafts: $n = 1$) with median (range) transplant mass per graft 5,830 (3,890–12,000) islet equivalents (IEQ)/kg body weight and overall transplant mass per recipient 11,232 (5,014–16,734) IEQ/kg. Median follow-up time was 18 (1–51) months posttransplant, and during this time,

participants underwent 5 (1–14) clinical assessments (Fig. 1).

All participants attained primary graft function at 1 month post-first transplant, evidenced by restoration of stimulated C-peptide >50 pmol/L. During follow-up, there was a wide range of stimulated C-peptide concentrations (7–2,622 pmol/L) both within and between individuals (Fig. 1). Restoration of endogenous β -cell function was associated with recovery of hypoglycemia awareness and resolution of recurrent severe hypoglycemia (Table 1). Overall, median HbA_{1c} improved and insulin dose was reduced, although again, range was wide, with only one recipient achieving and maintaining insulin independence (Table 1). Transplantation was not associated with deterioration in renal function.

Relationship of Blood Glucose Control With Endogenous C-Peptide Production

As endogenous β -cell function increased across the predefined C-peptide

Table 1—Islet recipient characteristics and metabolic parameters pre- and posttransplant

| | Pretransplant | Posttransplant | P value |
|--|------------------|-----------------------|---------|
| <i>N</i> | 12 | 12 | |
| Sex (female/male) (<i>n</i>) | 10/2 | 10/2 | |
| Recipient age (years) | 51.5 (44–64) | | |
| Diabetes duration (years) | 38.5 (5–43) | | |
| Insulin regimen (CSII/MDI/none) (<i>n</i>) | 5/7/0 | 4/7/1 | |
| Body weight (kg) | 61.7 (50.0–76.0) | | |
| ITA/IAK (<i>n</i>) | 9/3 | | |
| Total islet infusions received (<i>n</i>) | | 20 | |
| Number of islet infusions/recipient (<i>n</i>) | | 2 (1–3) | |
| Transplant mass (IEQ/kg per recipient) | | 11,232 (5,014–16,734) | |
| Donor age (years) | | 48 (23–59) | |
| Donor BMI (kg/m ²) | | 31.0 (23.0–35.6) | |
| Follow-up posttransplant (months) | | 18 (1–51) | |
| Assessments posttransplant (<i>n</i>) | | 5 (1–14) | |
| Severe hypoglycemia (episodes per person-year) | 12 (0–50) | 1 (0–3) | <0.01 |
| Clarke score | 7 (6–7) | 3 (1–6) | 0.03 |
| Gold score | 6 (4–7) | 2 (1–5) | 0.01 |
| HbA _{1c} (%) | 9.7 (5.9–12.9) | 7.4 (5.4–11.1) | <0.01 |
| HbA _{1c} (mmol/mol) | 83 (41–117) | 57 (36–98) | |
| Insulin requirement (units/kg) | 0.60 (0.42–1.04) | 0.42 (0–0.95) | <0.01 |
| Creatinine (μ mol/L) | 89 (57–157) | 99 (64–196) | 0.13 |
| MTT90 C-peptide (pmol/L) | | 483 (56–2,207) | |

Data are presented as median (range) or *n*. Posttransplant data are for duration of follow-up or for hypoglycemia all times posttransplant. CSII, continuous subcutaneous insulin infusion; IAK, islet after kidney; ITA, islet transplant alone; MDI, multiple daily insulin injections; MTT90, meal tolerance test at 90 min.

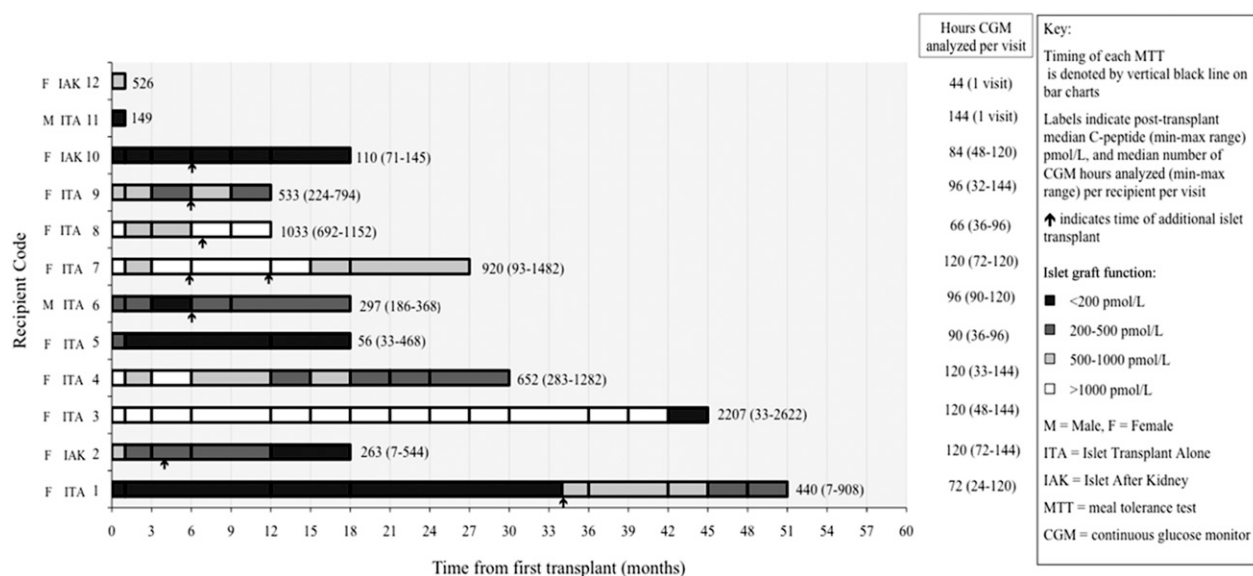


Figure 1—Bar chart showing islet graft function from time of first islet transplant in individual recipients, indicating timing of subsequent transplants. Endogenous C-peptide [median (range)] and CGM hours analyzed [median (range)] from posttransplant assessments are also reported for each recipient.

groups, exogenous insulin dose was reduced and HbA_{1c} improved (Table 2). Measures of glycemia assessed by CGM showed a similar relationship with mean glucose, SD blood glucose, duration of hypoglycemia, normoglycemia, and hyperglycemia, together with hypoglycemia and hyperglycemia risk indices all improving with increasing C-peptide across the groups (Table 2).

A mixed Poisson regression model demonstrated strong continuous associations between stimulated C-peptide and mean plasma-calibrated interstitial glucose (Fig. 2A), glucose SD (Fig. 2B), and time spent outside the target range (3.0–10.0 mmol/L) (Fig. 2C). For each 100-pmol/L increase in stimulated endogenous C-peptide, mean interstitial glucose decreased by 2.5% (95% CI 1.5–3.5%); SD of blood glucose was reduced by 4.9% (95% CI 3.4–6.4%); and proportion of time spent outside target glucose range (3.0–10.0 mmol/L) was reduced by 12.9% (95% CI 12.6–13.2%).

Similar continuous relationships were shown between stimulated C-peptide and complex measures of the quality of glycemic control, including ADRR and HBGI. For each 100-pmol/L increase in stimulated endogenous C-peptide, ADRR was reduced by 6.7% (95% CI 4.3–9.0%) (Fig. 2D), and mean HBGI was reduced by 9.5% (95% CI 6.8–12.2%) (Fig. 2E).

Percentage of time spent with low glucose (<3.0 mmol/L) was very small in all C-peptide groups posttransplantation at ≤0.5%, but significant reductions in duration of biochemical hypoglycemia and hypoglycemia risk determined by LBGI were still seen with increasing concentrations of C-peptide (Table 2 and Fig. 2F).

CONCLUSIONS

An intrinsic relationship between endogenous β-cell function and CGM parameters of improved overall glycemic control/reduced glucose variability has been demonstrated in islet transplant recipients. Studying this relatively homogeneous insulin-sensitive group with rapidly changing graft function over a short period of time confirmed incremental benefits through restoration of even low concentrations of stimulated C-peptide.

Evidence that attainment of C-peptide positivity following islet transplantation can restore hypoglycemia awareness and prevent recurrent severe hypoglycemia is now incontrovertible (6,27,28). As demonstrated again in the current study, this can be achieved even without insulin cessation.

Significant HbA_{1c} lowering is also an established benefit of a functioning islet transplant with previous studies showing that target (<7.0% [53 mmol/mol])

can be achieved both with and without sustained insulin independence (27). In this study, we have demonstrated a clear relationship between current level of endogenous β-cell function and HbA_{1c}, paralleled by incremental reduction in exogenous insulin dose. It is of particular interest that this relationship is seen even in a program in which maintenance of sufficient insulin doses to achieve optimal glycemic control in all recipients at all time points is actively promoted using optimized multiple daily insulin injection or continuous subcutaneous insulin infusion regimens, as opposed to an approach targeted toward insulin withdrawal/cessation. This provides further evidence for an intrinsic and acute impact of current β-cell function on overall glycemic control, in keeping with the findings in C-peptide-positive participants in the DCCT (8,9).

A greater understanding of the impact of endogenous C-peptide capacity on blood glucose parameters was obtained in the current study by parallel CGM analysis. Stratification of outcomes according to preagreed stimulated C-peptide groupings allowed initial assessment of the relationship with measures of metabolic control. When measured concentration of endogenous C-peptide declined in an islet transplant recipient, concomitant CGM profile revealed deterioration in

parameters of blood glucose control even if excellent graft function and desirable glucose control outcomes had been achieved previously.

CGM has been used in previous studies to confirm improved glucose control and reduced variability following islet transplantation (10,11–15). Most recently, the Lille group (29) used the Edmonton protocol to rapidly deliver two to three transplants per recipient (with median time between first and last transplant only 2 months) toward early attainment and maintenance of insulin independence. Significant improvements in mean glucose and glucose SD, together with reduced duration of both hyperglycemia and hypoglycemia using the same cutoffs as in the current study, were confirmed by CGM analysis. This group showed for the first time significant correlations between each of these measures and the β -score (a composite measure of graft function calculated from insulin dose, HbA_{1c}, fasting glucose, and MTT C-peptide) (10,30). In our analysis, we have modeled the relationships between parameters of glycemic control and a single universally applicable measure of current endogenous β -cell function (stimulated C-peptide in an MTT), confirming a continuous effect across a wide range of C-peptide values.

It appears that even low concentrations of endogenous C-peptide may be sufficient to substantially reduce risk of severe hypoglycemia. The Lille group (29) reported the need for restoration of virtually normal β -cell function (β -score 7 to 8) to truly normalize mean glucose, glucose SD, and biochemical hyperglycemia duration but showed that partial graft function was sufficient to virtually abolish biochemical hypoglycemia in recipients who were spending a median of 5% of time with glucose <3 mmol/L pretransplant. This is reflected in our own cohort with recurrent severe hypoglycemia and impaired awareness of hypoglycemia pretransplant but very low levels of biochemical hypoglycemia even in those with lowest concentrations of C-peptide posttransplant (median of 0.5% of time with glucose <3 mmol/L in those with posttransplant C-peptide <200 pmol/L).

In the current study, intrinsic relationships between absolute levels of endogenous β -cell function and more complex

Table 2—CGM outcomes in islet transplant recipients according to graft function

| MTT 90-min C-peptide category at time of CGM/clinical assessment | Trace analysis/recipient (n) | Glycemic control | | | | Mean glucose (mmol/L) | Glucose variability, SD (mmol/L) | Glycemic stability/risk indices | | | | HbA _{1c} /insulin dose |
|--|------------------------------|------------------------------|------------------------------------|-----------------------------------|----------------------------------|-------------------------------|------------------------------------|---------------------------------|----------------------------------|--------------------------------|------------------------------------|---------------------------------|
| | | Hypoglycemic (<3 mmol/L) (%) | Normal (3–10 mmol/L) (%) | Hyperglycemic (>10 mmol/L) (%) | Mean | | | ADRR | LBGI | HBGI | HbA _{1c} (%) | |
| Low (n = 19) (<200 pmol/L) (7–186) | 90 [58–120] (24–144) | 0.5 [0–2.4] (0–11.5) | 46.2 [28.9–75.2] (3.1–85.8) | 51.7 [24.8–71.1] (5.5–96.9) | 10.7 [8.6–12.9] (6.1–19.1) | 4.4 [3.2–5.6] (2.5–6.2) | 46.5 [35.1–52.8] (18.0–57.0) | 3.3 [1.2–8.0] (0–12.6) | 18.2 [7.6–24.0] (3.0–44.4) | 8.7 [8.1–9.4] (6.5–11.8) | 0.61 [0.53–0.82] (0.38–0.95) | |
| Moderate (n = 15) (200–500 pmol/L) (224–492) | 108 [90–120] (32–144) | 0 [0–1.5] (0–8.1) | 57.7 [43.0–72.7] (22.9–99.1) | 41.7 [26.7–57.0] (0.9–76.7) | 9.6 [8.1–10.4] (5.9–14.0) | 2.6 [2.1–3.7] (1.4–5.1) | 32.2 [19.9–33.6] (6.6–55.1) | 2.6 [1.1–5.3] (0–10.7) | 10.1 [5.9–14.1] (1.5–27.8) | 7.6 [7.0–7.9] (4.8–10.0) | 0.41 [0.24–0.44] (0.22–0.58) | |
| Good (n = 17) (500–1,000 pmol/L) (526–920) | 96 [78–120] (44–144) | 0 [0–0.6] (0–2.1) | 75.4 [59.9–96.7] (15.2–98.8) | 21.3 [3.1–40.1] (1.2–84.9) | 8.6 [6.7–9.9] (6.2–12.8) | 2.2 [1.7–2.8] (1.4–4.3) | 19.8 [9.6–36.8] (5.2–49.0) | 2.6 [0.5–3.9] (0–6.7) | 6.0 [2.5–10.9] (1.8–19.2) | 6.9 [6.5–7.5] (5.2–8.1) | 0.33 [0.22–0.47] (0.18–0.64) | |
| Excellent (n = 23) (>1,000 pmol/L) (1,033–2,622) | 120 [96–120] (36–144) | 0 [0–0] (0–0.3) | 94.7 [87.4–98.8] (59.7–99.9) | 5.3 [1.2–12.2] (0.1–40.2) | 7.5 [7.0–7.9] (6.5–9.7) | 1.4 [1.1–1.8] (0.8–3.5) | 12.1 [8.2–19.0] (6.0–31.6) | 0.5 [0.2–1.0] (0–3.3) | 2.6 [1.7–4.1] (1.2–9.7) | 6.3 [6.1–6.8] (5.2–9.1) | 0 [0–0.46] (0–0.56) | |

Data are presented as median [interquartile range] (range), n, total number of MTIs included within each group.

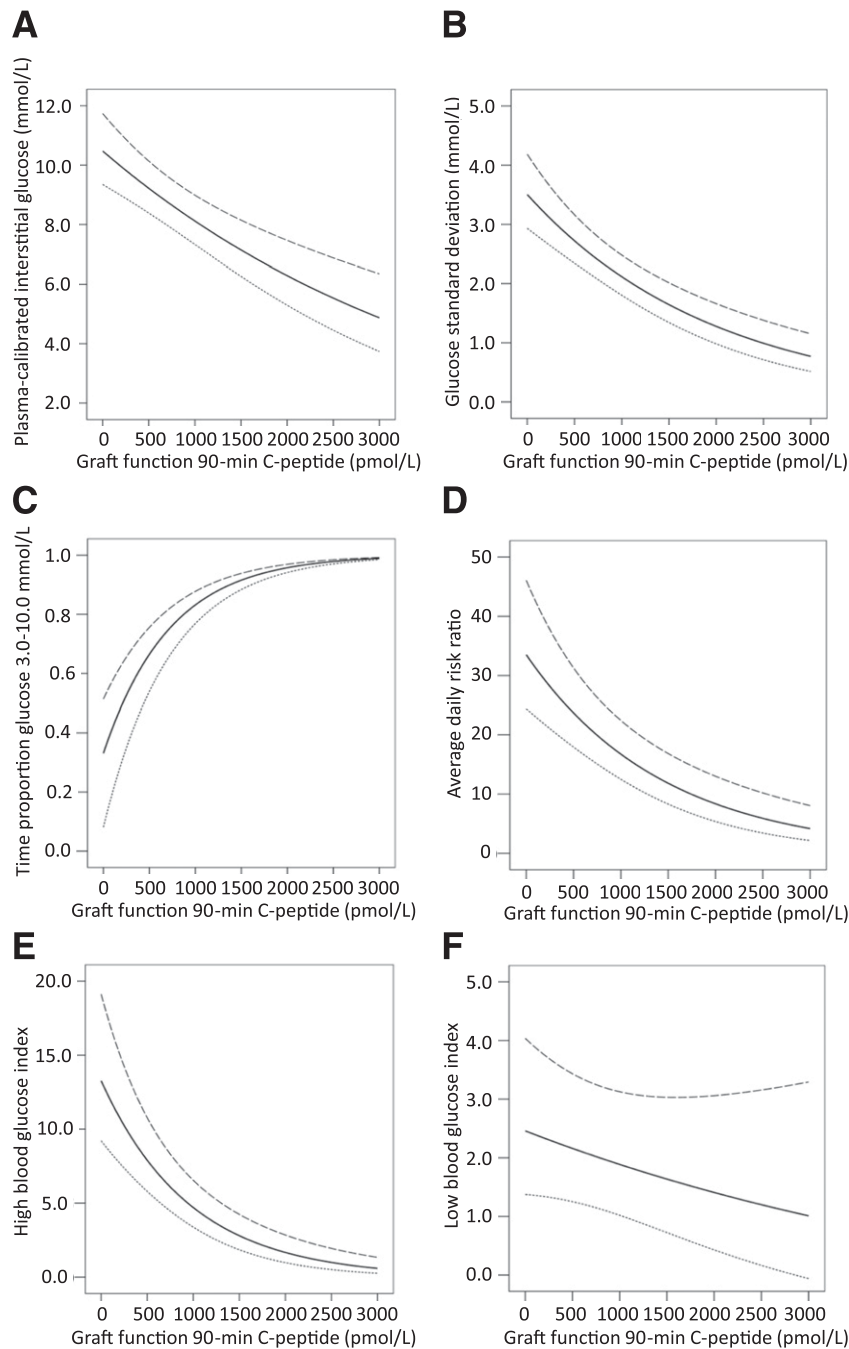


Figure 2—Regression model plots showing relationship of endogenous C-peptide production with mean plasma-calibrated interstitial glucose (A); glucose SD (B); proportion of time spent within target range (3.0–10.0 mmol/L) (C); ADRR (D); HBGI (E); and LBGI (F). Solid line: predicted values; long dashed line: upper 95% CI; short dashed line: lower 95% CI.

measures of quality of glucose control associated with hyperglycemia and hypoglycemia risk were also demonstrated. LBGI and HBGI split overall glucose variation into two independent sections related to excursions into hypoglycemia and hyperglycemia, equalizing the amplitude of the excursions with respect to the risk they carry (24). ADRR is designed to be equally sensitive to

hypoglycemia and hyperglycemia risk (20), taking into account the asymmetric nature of the blood glucose scale and providing a measure of event severity. Regression analysis demonstrated a continuous relationship with endogenous C-peptide capacity for both HBGI and ADRR. Significant reduction in hypoglycemia risk was also achieved with increasing concentration of C-peptide, but

LBGI was small at all C-peptide concentrations and CIs were wide, in keeping with the very low duration of hypoglycemia in all posttransplant recipients.

The relationships we have described and the regression analyses performed indicate that even low concentrations of C-peptide below the threshold reported in DCCT (200 pmol/L) are likely to have a positive impact on measures of glycemic control. This supports the findings of a recently published study that used glucose clamps to assess functional β -cell mass in islet recipients, demonstrating a correlation among HbA_{1c}, insulin dose, and glycemic variability even at low levels of β -cell function (31). Functional β -cell mass <5% was not associated with measurable improvement in fasting glucose variability, and whether very low concentrations of C-peptide (<50 pmol/L) have meaningful effect will require further study. Reanalysis of DCCT data in shorter duration type 1 diabetes has also shown a near-linear relationship of C-peptide (without a discernible lower limit) with insulin dose, hypoglycemia risk, HbA_{1c}, and retinopathy (9).

Repeated measures in a relatively small cohort may be perceived as a weakness of our study, and absolute glucose values must be interpreted with caution given the limitations of current CGM sensors (32–34). However, studying islet transplant recipients with long-standing experience of optimized self-management for established type 1 diabetes has enabled unique insights into the intrinsic impact of changes in endogenous β -cell function in the absence of confounding educational or insulin treatment interventions. While it may be possible to extrapolate these findings to nontransplant insulin-sensitive patients with normal renal function, the current findings are restricted to a relatively narrow cohort with long-duration disease.

In conclusion, repeated assessment of islet transplant recipients as C-peptide changed over time has enabled detailed modeling of the relationship between current endogenous β -cell function and multiple parameters of overall glycemic control. Clinical benefits in terms of improved hypoglycemia awareness and reduced severe hypoglycemia, together with incremental reductions in exogenous insulin requirement

and HbA_{1c} as C-peptide concentrations increase, have been confirmed. Moreover, this study has provided quantitative estimates of the expected impact of a given stimulated C-peptide concentration on mean glucose, time within range, and glucose variability in individuals with type 1 diabetes.

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tolerance tests; designed and conducted the analysis; and wrote the first draft of the manuscript. N.S. undertook collation and analysis of CGM outcome data (in collaboration with Newcastle University Department of Statistics), designed and conducted the analysis, and wrote the first draft of the manuscript. J.A.M.S. contributed to study design and data interpretation, coordinating study completion and data collection; led in designing, analyzing, and interpreting meal tolerance tests; designed and conducted the analysis; and wrote the first draft of the manuscript. This study was conceived, managed, and interpreted jointly by all authors, and all authors contributed to and approved the final version of the manuscript. J.A.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.

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