Restoration of Glucose Counterregulation by Islet Transplantation in Long-Standing Type 1 Diabetes

Short title: Islet Transplants and Glucose Counterregulation

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Abstract

Patients with long-standing type 1 diabetes (T1D) may exhibit defective glucose counterregulation and impaired hypoglycemia symptom recognition that substantially increase their risk for experiencing severe hypoglycemia. To determine whether intrahepatic islet transplantation improves endogenous glucose production (EGP) in response to hypoglycemia in T1D patients experiencing severe hypoglycemia, we studied subjects (n=12) longitudinally with ~30 years disease duration before and 6 months after intrahepatic islet transplantation using stepped hyperinsulinemic-hypoglycemic and paired hyperinsulinemic-euglycemic clamps with infusion of 6,6-$^2$H$_2$-glucose, and compared results to those from a nondiabetic control group (n=8). Following islet transplantation, HbA$_{1c}$ was normalized and time spent hypoglycemic (<70 mg/dl) was nearly abolished as indicated by continuous glucose monitoring. In response to insulin-induced hypoglycemia, C-peptide (absent prior to transplant) was appropriately suppressed, glucagon secretion was recovered, and epinephrine secretion was improved after transplantation. Corresponding to these hormonal changes, the EGP response to insulin-induced hypoglycemia, absent before, was normalized following transplantation, with a similar effect seen for autonomic symptoms. Since the ability to increase EGP is ultimately required to circumvent the development of hypoglycemia, these results evidence that intrahepatic islet transplantation can restore glucose counterregulation in long-standing T1D, and support its consideration as treatment for patients with hypoglycemia unawareness experiencing severe hypoglycemia.
Defective glucose counterregulation develops in long-standing type 1 diabetes (T1D) due to progressive impairments in defense mechanisms against a falling plasma glucose concentration in the setting of therapeutic hyperinsulinemia(1). This includes loss of inhibition in endogenous insulin secretion, with associated loss of activation in glucagon secretion, which together normally serve to increase endogenous (primarily hepatic) glucose production (EGP), and impairment in sympathoadrenal epinephrine secretion, which contributes to EGP, and symptom generation, which leads to a syndrome of hypoglycemia unawareness also known as hypoglycemia-associated autonomic failure (HAAF(2)). Hypoglycemia unawareness in T1D is associated with a twenty-fold increased risk for experiencing severe hypoglycemia(3), which itself contributes importantly to increased morbidity(4) mortality(5).

In cross-sectional studies of long-standing T1D, following intrahepatic islet transplantation insulin-induced hypoglycemia is associated with normal inhibition of endogenous insulin secretion, and either defective or partially restored glucagon secretion, epinephrine secretion, and symptom responses(6-8). We sought to determine whether the recovery of islet responses to hypoglycemia following transplantation together with avoidance of hypoglycemia afforded by functioning islet grafts would reverse HAAF and restore the EGP response by studying longitudinally the same patients before and 6-months after transplantation.

RESEARCH DESIGN AND METHODS
Subjects included had long-standing C-peptide negative T1D complicated by hypoglycemia unawareness and frequent severe hypoglycemia events who underwent islet alone transplantation (n=12) as part of the Clinical Islet Transplantation (CIT) Consortium protocols conducted at the University of Pennsylvania. These included all eleven subjects participating in the CIT07
protocol from our institution(9) and one of two participants who experienced early islet graft failure with the CIT05 protocol that included rituximab for induction and was later re-transplanted under an Edmonton protocol(10). The transplant recipients underwent one or two intraportal infusions of islets in order to achieve insulin-independence.

Healthy nondiabetic control subjects (n=8) were sex, age, and BMI-matched to the T1D subjects. The study protocols were approved by the Institutional Review Board of the University of Pennsylvania, and all subjects gave their written informed consent to participate.

Continuous Glucose Monitoring
T1D subjects were evaluated using a 72 hour continuous glucose monitoring system (CGMS; Medtronic Minimed) prior to and at 75 days following islet transplantation.

Metabolic Studies
T1D subjects underwent randomized-paired hyperinsulinemic-hypoglycemic and euglycemic clamps before and between 6-7 months after transplantation, each following an overnight fast after 2000 for 12 h before testing. At \( t = -120 \) min a primed (5 mg/kg·fasting plasma glucose in mg/dl/90 for 5-min) continuous (0.05 mg·kg\(^{-1}\)·min\(^{-1}\) for 355-min) infusion of the stable glucose isotope tracer 6,6-\(^2\)H\(_2\)-glucose (99% enriched; Cambridge Isotopes Laboratories, Andover, MA) was administered to assess EGP before and during the induction of hyperinsulinemia(11). When necessary overnight to target the baseline blood glucose at 81–115 mg/dl, a low-dose insulin infusion was continued during this period to maintain stable normoglycemia until \( t = 0 \). After baseline blood sampling at -20, -10, and -1 min, at \( t = 0 \) min a continuous infusion of insulin was initiated at 1 mU·kg\(^{-1}\)·min\(^{-1}\) for 240-min. Subsequently, a variable rate infusion of 20% glucose
was administered to either achieve hourly plasma glucose steps of ~80, 65, 55, and 45-mg/dl for the hypoglycemic clamp, or to maintain the plasma glucose ~90 mg/dl for the euglycemic clamp(12). To reduce changes in plasma enrichment of 6,6-\(^2\)H\(_2\)-glucose during the clamp, the 20% glucose solution was enriched to ~2.0% with 6,6-\(^2\)H\(_2\)-glucose(11). Plasma glucose was measured every 5-min at bedside with an automated glucose analyzer (YSI 2300; Yellow Springs Instruments) to adjust the glucose infusion rate and achieve the desired concentration. Additional blood samples and an autonomic symptom questionnaire were collected every 20-min and analyzed as previously described(7,8,10). Samples from paired hypoglycemic-euglycemic experiments of each subject pre- and 6-months post-transplant were assayed simultaneously.

**Calculations and statistics.** The rate of appearance (Ra) of glucose during the clamps was calculated using Steele’s non-steady state equation modified for the use of stable isotopes as previously described(10). EGP was calculated from the difference between the Ra of glucose in the plasma and the infusion rate of exogenous glucose. The magnitude of each hormonal, EGP, free fatty acid, and incremental symptom response was assessed as the mean of values obtained during the last 60-min of hypoglycemia.

All data are expressed as mean±SE. Comparison of results between pre- and post-transplant T1D subjects and between each T1D group and controls were performed with paired or unpaired Student’s \(t\) tests or the corresponding nonparametric test as appropriate using Statistica software (StatSoft, Inc.). Significance was considered at \(P<0.05\) (two-tailed).
RESULTS

Subject characteristics and continuous glucose monitoring. The T1D subjects were of comparable gender distribution, age, body weight, and body mass index (BMI) with the nondiabetic control subjects (Table 1). HbA$_{1c}$, which was elevated before, decreased to nondiabetic levels after islet transplantation ($P$<0.01; Table 1). The T1D subjects had ~30 years of disease duration and an insulin requirement of ~0.5 U·kg$^{-1}$·d$^{-1}$ that was substantially reduced ($P$<0.01; Table 1) after the receipt of 9,648±666 islet equivalents per kilogram recipient body weight. Seven subjects were insulin-independent following one islet infusion, three were insulin independent following two islet infusions, one was insulin-dependent while awaiting a second islet infusion, and one remained insulin-dependent after two islet infusions. Subjects maintained appropriate levels of tacrolimus and sirolimus (Table 1).

The selection of T1D subjects for the presence of hypoglycemia unawareness, severe hypoglycemia, and marked glycemic lability was reflected in the substantially elevated Clarke score(12), HYPO score(13), and lability index (LI(13)), respectively, before transplantation (Table 1). Following transplantation, the Clarke score of reduced hypoglycemia awareness became negligible, glycemic lability was markedly reduced, and CGMS demonstrated substantial reductions in mean glucose (164±11 to 121±4 mg/dl; $P$<0.01), glucose SD (73±6 to 23±4 mg/dl; $P$<0.01), and time spent hyperglycemic (glucose >180 mg/dl; 38±5 to 4±3 %; $P$<0.01), with essentially no time spent hypoglycemic (glucose <70 mg/dl; 12±2 to 2±1 %; $P$<0.01) ((14)Supplemental Fig.).
**Insulin and glucose during the hypoglycemic and euglycemic clamps.** The insulin infusion during the hypoglycemic clamp resulted in comparable hyperinsulinemia in the T1D subjects before and after transplantation (99±14 vs. 79±5 μU/ml), and in the controls (84±8 μU/ml), which was also not different in any group from the hyperinsulinemia achieved during their respective euglycemic control experiments. During the hypoglycemic clamp, plasma glucose by 60-min was near 80 mg/dl in all three groups, and thereafter overlapped during the 65, 55, and 45-mg/dl hourly glucose steps, whereas during the euglycemic clamp, plasma glucose remained between 85–90 mg/dl.

**Islet cell hormonal responses.** Endogenous insulin secretion, as measured by C-peptide, was inhibited by hyperinsulinemia during the euglycemic clamp similarly in both the T1D subjects after transplantation and in controls, with identical complete suppression occurring during hypoglycemia (Fig 1A; Table 2). Glucagon was suppressed during hypoglycemia in the T1D subjects before transplantation (P<0.01 compared to controls) to levels not different than under euglycemic conditions, whereas glucagon increased during hypoglycemia in the T1D subjects after transplantation (P<0.01), albeit to levels that remained less than in controls (P<0.05; Fig. 1B; Table 2). Pancreatic polypeptide failed to activate in the T1D subjects before transplantation, but did respond to hypoglycemia after transplantation (P<0.05), although again to levels less than in controls (P<0.05; Fig. 1C; Table 2).

**Sympathoadrenal responses.** Epinephrine secretion was markedly impaired during hypoglycemia in the T1D subjects before transplantation (P<0.01 compared to controls), and improved after transplantation (P<0.01), but the magnitude of the response remained less than in
controls ($P<0.01$; Fig. 2A; Table 2). Autonomic symptoms were also diminished during hypoglycemia in the T1D subjects before transplantation ($P<0.05$ compared to controls), with a trend toward improved symptom responses after transplantation ($P=0.06$) that were not different from that in controls (Fig. 2B; Table 2).

**EGP and free fatty acids.** EGP was suppressed during hypoglycemia in the T1D subjects before transplantation ($P<0.01$ compared to controls) to levels not different than under euglycemic conditions, whereas EGP increased in response to hypoglycemia after transplantation ($P<0.05$) such that the magnitude of the response was not different than in controls (Fig. 2C; Table 2). Free fatty acids were suppressed during hypoglycemia in the T1D subjects before transplantation ($P<0.01$ compared to controls), but increased in response to hypoglycemia after transplantation ($P<0.05$) such that the magnitude of the response was not different than in controls (Table 2).

**DISCUSSION**

The present study demonstrates that intrahepatic islet transplantation can restore glucose counterregulation and improve hypoglycemia symptom recognition in patients with long-standing T1D. These are the first data to show that the EGP response to insulin-induced hypoglycemia, absent in our patients with long-standing T1D prior to transplantation, was normalized by 6-months following transplantation. Since the ability to increase EGP is what is ultimately required to circumvent the development of low blood glucose, this finding helps to explain the dramatic effect of clinical islet transplantation on the amelioration of problematic hypoglycemia in T1D patients with severe hypoglycemia unawareness.
These results extend by longitudinal design prior cross-sectional studies indicating that intrahepatic islets respond appropriately to insulin-induced hypoglycemia by suppressing endogenous insulin secretion(6,7) and partially restoring glucagon(7) and epinephrine secretion(8). That the magnitude of the glucagon response is less than normal may be explained by the mass of surviving islets being less than normal as estimated by measurement of the β-cell secretory capacity. In fact, the glucagon response after islet transplantation reported here appears greater than in our prior studies(7,8), and is consistent with the significant improvement in β-cell secretory capacity to ~40–50% of normal we have reported using the CIT07 protocol for islet transplantation(9). While epinephrine can augment glucagon secretion(15), it reasons that the glucagon response is from transplanted rather than native islets because patients with long-standing T1D who have normal epinephrine responses to insulin-induced hypoglycemia still fail to release glucagon(16). An alternative explanation for the partial glucagon response posits inhibition of intrahepatic α-cells by the resulting increased EGP as local glucose levels may be higher than that measured peripherally(17). However, the normal suppression of C-peptide during hypoglycemia indicates that intrahepatic β-cells do appropriately sense and respond to the degree of peripheral hypoglycemia. Whether alternative sites for islet transplantation may allow for greater glucagon responses(18) and glucose counterregulation requires further study.

Abolition of hypoglycemia following islet transplantation was documented by CGMS indicating almost no time spent <70 mg/dl. This finding is consistent with prior reports on glycemic control evaluated by CGMS in islet recipients, including a large number of subjects utilizing insulin to maintain near-normoglycemia(19-21). The avoidance of time spent hypoglycemic would be expected to ameliorate HAAF. Indeed, the markedly impaired
epinephrine secretion prior to transplantation was significantly improved following transplantation, and autonomic symptoms, also impaired prior to transplantation, improved by trend and were not different from controls following transplantation. Pancreatic polypeptide secretion, a marker of parasympathetic (vagal) activation of the islet that failed to activate before transplantation, did respond to hypoglycemia after islet transplantation, and likely represents another marker for reversal of HAAF(16).

That the partially normal glucagon and epinephrine responses were associated with complete normalization of the EGP response to insulin-induced hypoglycemia may be explained by the change in glucagon level, rather than its absolute concentration, being most important for stimulating EGP in humans(22), and that glucagon and epinephrine operate synergistically to increase EGP(23). The increase in free fatty acids during insulin-induced hypoglycemia after, but not before, transplantation suggests correction of defective activation of lipolysis best explained by the improved epinephrine(24). Free fatty acids are an important fuel substrate for glucose production by the liver, and together with the effects of improved glucagon and epinephrine on the liver likely contributed to restoration of the EGP response. Our results are consistent with those of a recent cross-sectional study that included intrahepatic islet transplant recipients with partial graft function associated with partial restoration of the EGP response to insulin-induced hypoglycemia(25), suggesting a threshold for counterregulatory hormone responses may exist for normalization of EGP.

In conclusion, intrahepatic islet transplantation can restore glucose counterregulation and improve hypoglycemia symptom recognition in patients with long-standing T1D. While the adverse effects of the required immunosuppression preclude broad application in T1D, and further work should establish the durability of improved glucose counterregulation, islet
transplantation should be considered as a treatment option for patients with severely problematic hypoglycemia.

ACKNOWLEDGMENTS

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No potential conflicts of interest relevant to this article were reported.

M.R.R. designed and conducted the study, researched data, and wrote the manuscript, C.F., C.D.-B., E.M., M.P., K.C., and J.T. participated in the conduct of the study, researched data, and reviewed/edited the manuscript, S.K. researched data, and reviewed/edited the manuscript, C.L. participated in the conduct of the study, researched data, and reviewed/edited
the manuscript, A.N. contributed to the design and conducted the study, researched data, and revised the manuscript critically for important intellectual content, K.L.T. contributed to the design of the study, researched and analyzed data, and revised the manuscript critically for important intellectual content. M.R.R. is the guarantor of this work and, as such, takes full responsibility for the work as a whole, including the study design, access to data, and the decision to submit and publish the manuscript.

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FIG. 1. Islet cell hormonal responses during the hyperinsulinemic hypoglycemic clamp in type 1 diabetes subjects before (-○-) and 6 months following (-▲-) islet transplantation (n = 12), and in nondiabetic control subjects (-■-, n = 8). For C-peptide (A), data are not shown before transplantation when undetectable (< 0.1 ng/ml), and the response during the euglycemic clamps is shown for the type 1 diabetes subjects 6 months following transplantation (-Δ-, n = 12), and in the control group (-□-, n = 8). For glucagon (B) and pancreatic polypeptide (C) the shaded area represents the 95% confidence interval for data derived from all the hyperinsulinemic euglycemic control experiments (n = 32).

FIG. 2. Sympathoadrenal (epinephrine, A, and autonomic symptoms, B), and endogenous glucose production (C) responses during the hyperinsulinemic hypoglycemic clamp in type 1
diabetes subjects before (-○-) and 6 months following (-▲-) islet transplantation (n = 12), and in nondiabetic control subjects (-■-, n = 8, except for epinephrine where n = 6). The shaded area represents the 95% confidence interval for data derived from the hyperinsulinemic euglycemic control experiments (n = 32, except for epinephrine where n = 30).

TABLE 1
Subject characteristics.

<table>
<thead>
<tr>
<th></th>
<th>T1D subjects, before islet transplantation</th>
<th>T1D subjects, after islet transplantation</th>
<th>Nondiabetic control subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male/female</td>
<td>5/7</td>
<td>5/7</td>
<td>4/4</td>
</tr>
<tr>
<td>Age (years)</td>
<td>45 ± 3</td>
<td>47 ± 3**</td>
<td>44 ± 3</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>71 ± 3</td>
<td>65 ± 3**</td>
<td>77 ± 5</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25 ± 1</td>
<td>23 ± 1**</td>
<td>25 ± 1</td>
</tr>
<tr>
<td>HbA₁c (%)¹</td>
<td>7.1 ± 0.2</td>
<td>5.6 ± 0.1**</td>
<td>5.5 ± 0.1**</td>
</tr>
<tr>
<td>T1D duration (years)</td>
<td>29 ± 4</td>
<td>31 ± 4**</td>
<td>—</td>
</tr>
<tr>
<td>Insulin use (U·kg⁻¹·d⁻¹)</td>
<td>0.48 ± 0.05</td>
<td>0.06 ± 0.05**</td>
<td>—</td>
</tr>
<tr>
<td>Response</td>
<td>T1D subjects, before Islet Transplantation</td>
<td>T1D subjects, after Islet Transplantation</td>
<td>Nondiabetic control subjects</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>------------------------------------------</td>
<td>------------------------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>n</td>
<td>12</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>C-peptide (ng/ml)</td>
<td>—</td>
<td>0.16 ± 0.02</td>
<td>0.13 ± 0.01</td>
</tr>
<tr>
<td>Glucagon (pg/ml)</td>
<td>33 ± 3</td>
<td>60 ± 7**</td>
<td>95 ± 13**</td>
</tr>
<tr>
<td>PP (pmol/l)</td>
<td>32 ± 8</td>
<td>76 ± 23*</td>
<td>160 ± 16**†</td>
</tr>
<tr>
<td>Epinephrine (pg/ml)</td>
<td>130 ± 16</td>
<td>253 ± 21**</td>
<td>419 ± 46**‡</td>
</tr>
<tr>
<td>Autonomic symptoms (∆)</td>
<td>2.2 ± 0.9</td>
<td>5.3 ± 1.0 §</td>
<td>6.9 ± 2.4*</td>
</tr>
<tr>
<td>EGP (mg·kg⁻¹·min⁻¹)</td>
<td>0.59 ± 0.12</td>
<td>1.18 ± 0.13*</td>
<td>1.42 ± 0.14**</td>
</tr>
</tbody>
</table>

Data are means ± SE. T1D, type 1 diabetes; IE, islet equivalent whereby an IE approximates a standard islet diameter of 150 μm; IE/kg, IE transplanted per kilogram of recipient body weight. ND, not done.

aTo convert to mmol/mol, multiply by 10.93 and subtract 23.50.

bOne subject was converted from sirolimus to mycophenolate mofetil due to the development of interstitial pneumonia 4 weeks after transplant that subsequently resolved (9).

cClarke score of hypoglycemia unawareness (7 most, 0 none (12)).

dHYPO score of hypoglycemia severity developed by Ryan et al. (13).

eLability Index measure of glycemic lability developed by Ryan et al. (13).

** P < 0.01 for comparison to T1D subjects before transplantation.
<table>
<thead>
<tr>
<th>Free fatty acids (μmol/l)</th>
<th>50 ± 7</th>
<th>161 ± 37*</th>
<th>114 ± 18**</th>
</tr>
</thead>
</table>

Data are means ± SE. PP, pancreatic polypeptide; EGP, endogenous glucose production. aThe magnitude of each hormonal, endogenous glucose production, free fatty acid, and incremental symptom responses to the hypoglycemic clamps was assessed as the mean of values obtained during the last 60-min of each clamp. b n = 6 for epinephrine.

*P < 0.05 for comparison to T1D subjects before transplantation.

** P < 0.01 for comparison to T1D subjects before transplantation.

§P = 0.06 for comparison to T1D subjects before transplantation.

†P < 0.05 for comparison to T1D subjects after islet transplantation.

‡P < 0.01 for comparison to T1D subjects after islet transplantation.
FIGURE 1

A. C-PEPTIDE (ng/mL) over time for different conditions:
- Hypoglycemic Clamp Normal
- Euglycemic Clamp Normal
- Hypoglycemic Clamp Post-Transplant
- Euglycemic Clamp Post-Transplant

B. GLUCAGON (pg/mL) over time for different conditions:
- Hypoglycemic Clamp Pre-Transplant
- Hypoglycemic Clamp Post-Transplant
- Hypoglycemic Clamp Normal

C. PANCREATIC POLYPEPTIDE (pmol/L) over time for different conditions:
- Hypoglycemic Clamp Pre-Transplant
- Hypoglycemic Clamp Post-Transplant
- Hypoglycemic Clamp Normal
FIGURE 2

A. Hypoglycemic Clamp Pre-Transplant, Hypoglycemic Clamp Post-Transplant, Hypoglycemic Clamp Normal. EPINEPHRINE (pg/mL) vs. MINUTES.

B. Hypoglycemic Clamp Pre-transplant, Hypoglycemic Clamp Post-transplant, Hypoglycemic Clamp Normal. ◄ AUTONOMIC SYMPTOM SCORE vs. MINUTES.

C. Hypoglycemic Clamp Pre-Transplant, Hypoglycemic Clamp Post-Transplant, Hypoglycemic Clamp Normal. Endogenous Glucose Production (mg.kg⁻¹.min⁻¹) vs. MINUTES.
Supplementary Fig. Representative continuous glucose monitoring from a type 1 diabetes subject before (A) and 75 days following (B) islet transplantation after discontinuing exogenous insulin. Each color represents the interstitial glucose concentration throughout an individual day during a 72-hour recording interval. In panel A, interstitial glucose measured < 40 mg/dl is imputed at 40 mg/dl, the lower limit of detection ascribed to the glucose sensor.