Continuous Glucose Monitoring Metrics in Islet Transplant Recipients with Long-Term Insulin Independence

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Introduction

Islet transplantation is an effective treatment option for the management of type 1 diabetes in adult patients with hypoglycemia unawareness and episodes of severe hypoglycemia.

The advent of continuous glucose monitoring (CGM) has allowed for a better understanding and interpretation of glycemic profiles and variability and for determination of time-in-range metrics. Current recommended CGM time-in-range goals for adult type 1 diabetic subjects on a Hybrid-closed loop system are:

- 70-180 mg/dL: ≥ 70%
- <70 mg/dl: ≤ 3%
- <54 mg/dL: ≤1%

Notably, continuous glucose monitoring (CGM) in islet transplant recipients has shown improvement in time-in-range, reduction in glycemic variability (GV) and hypoglycemia prevention despite subnormal beta-cell function.

However, it is unclear if improvement in glycemic control and glucose variability as assessed by CGM metrics persists long-term in insulin independent islet transplant recipients.

Methods

We evaluated 5 islet transplant recipients who underwent intrahepatic islet transplantation at our institution between 2002-2010. Baseline characteristics and transplant related data are shown in **Table-1.**

Induction immunosuppression for subjects who received a 2nd islet infusion consisted of either daclizumab or basiliximab.

Data presented correspond to the last follow up study visit. Assessment of graft function and metabolic control included mixed meal tolerance tests for fasting and 90 minute glucose and C-peptide, HbA1c, Clarke score (a validated questionnaire for evaluation of hypoglycemia awareness with values ≥4 consistent with hypoglycemia unawareness), and BETA-2 score (composite measure of beta-cell function after ITx with scores ranging from 0 to 42, lower scores indicating higher risks of glucose intolerance and insulin dependence).

All subjects completed a 7-day non-blinded CGM (Dexcom® G4). At time of CGM, subjects were insulin independent and 10.7±3.5 years post-ITx (range 7.7-16.0). Two subjects were on non-insulin adjunct therapies (Linagliptin subject 1, and metformin subject 5).

Results

CGM metrics are shown in **Table 2**. Results (mean±SD) were as follows: sensor glucose 116±11 mg/dL; time in range 70-180 mg/dL: 96.4±3.0%; time in glucose <70mg/dL: 0.9±1.0%; and time in glucose <54 mg/dL: 0.1±0.1%. In addition, time in the more stringent glucose range of 70-140 mg/dL was 83.1±12.3%.

Figure 1 shows the 24hr CGM tracings averaged over a 7-days period for the 5 subjects.

Mixed meal tolerance test showed fasting C-peptide 1.4±0.2 ng/mL, 90 min C-peptide 4.8±1.2 ng/mL, fasting glucose 102±12 mg/dL and 90 min glucose 139±23 mg/dL (table 3).

Average HbA1c was 5.7±0.4% and Clarke score was 0 consistent with resolution of hypoglycemia.

Average BETA-2 score was 22±4 (values ≥ 20 associated with normal glucose tolerance and insulin independence).

Table 1. Baseline characteristics and transplantation related data

Subject #	Age (years)	Diabetes duration (years)	HbA1c (%)	Insulin dose (U/Kg/day)	Clarke Score	Islet infusions (#)	Total IEQ/Kg	Induction IS	Initial maintenance IS	Current maintenance IS
1	67	20	7.8	0.40	7	2	15,008	Daclizumab	siro & tacro	tacro & MMF
2	61	43	7.0	0.39	≥4	2	16,814	Alemtuzumab	siro & MMF	siro & MMF
3	50	37	8.0	0.51	6	1	11,435	Thymoglobulin	siro & tacro	siro & tacro
4	52	31	7.0	0.55	4	2	11,232	Thymoglobulin	siro & tacro	siro & tacro
5	60	42	5.0	0.36	5	2	17,179	Thymoglobulin	siro & tacro	siro & MMF
Mean	58.0	34.6	7.0	0.44	5.50	1.80	14,334			
SD	7.0	9.4	1.2	0.08	1.29	0.45	2,860			

IEQ = Islet equivalents
IS = immunosuppression
Siro = sirolimus
tacro = tacrolimus
MMF = mycophenolate mofetil
ATG = thymoglobulin

Table 2. Continuous glucose monitoring metrics

Subject #	Time post-ITx (years)	Average SG (mg/dL)	SG SD (mg/dL)	CV (%)	%Time <54 mg/dL	%Time <60 mg/dL	%Time <70 mg/dL	%Time 70-140 mg/dL	%Time 70-180 mg/dL	%Time >180 mg/dL	%Time >250 mg/dL	Time CGM active (%)
1	16.0	113	19	17.1	0	0	0.6	91.3	98.3	1.1	0	98.1
2	12.3	133	29	21.9	0	0	0	65.6	92.9	7.1	0.2	97.6
3	8.0	106	18	16.9	0.2	0.3	0.8	94.5	99.2	0	0	99.3
4	7.7	119	30	25.5	0	0	2.6	75.0	93.3	4.1	0	89.5
5	9.7	110	23	20.4	0.2	0.3	0.4	88.9	98.2	1.5	0	98.3
Mean	10.7	116	24	20.4	0.1	0.1	0.9	83.1	96.4	2.8	0.0	96.6
SD	3.5	11	6	3.6	0.1	0.2	1.0	12.3	3.0	2.9	0.1	4.0

ITx = Islet transplantation
SG= Sensor glucose
CV = coefficient of variation
MMTT = Mixed meal tolerance test

Results

Table 3. Mixed meal tolerance test, Clarke score and BETA-2 score

Subject #	Time post-ITx (years)	MMTT Fasting glucose (mg/dL)	MMTT 90 min glucose (mg/dL)	MMTT Fasting C-pep (ng/mL)	MMTT 90min C-pep (ng/mL)	HbA1c (%)	Clarke score	BETA-2 score
1	16.4	93	158	1.21	6.84	6.0	0	21
2	12.3	109	121	1.37	4.13	6.0	0	19
3	8.0	100	108	1.33	4.05	5.7	0	21
4	7.7	119	147	1.75	3.93	5.9	0	20
5	9.7	90	160	1.45	5.12	5.0	0	28
Mean	**10.7**	102	139	1.4	4.8	5.7		22
SD	**3.5**	12	23	0.2	1.2	0.4		4

MMTT = Mixed meal tolerance test

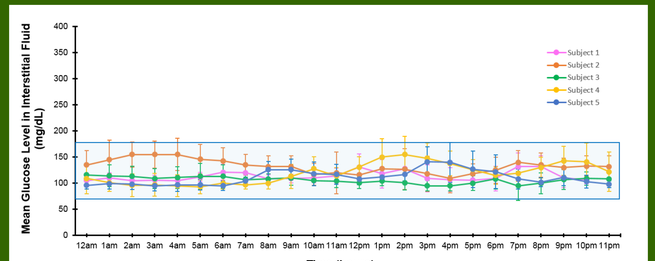

Figure 1. Continuous glucose monitoring tracings of 5 islet transplant recipients with long-term insulin independence
Data points represent the continuous glucose monitoring hourly average over a 7-day period. Error bars indicate standard deviations. The blue shaded area shows the glucose range of 70 to 180 mg/dL.

Conclusions

- In insulin independent islet transplant recipients with very good long-term graft function (BETA-2 score>15) and restoration of hypoglycemia awareness, CGM shows near-normalization of time-in-range, improved glycemic variability, and minimal time-in-hypoglycemia.
- Islet transplantation is a successful long-term cellular therapy for T1D in a selected group of patients.

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