Journal of Diabetes Science and Technology
Volume 2, Issue 2, March 2008

ORIGINAL ARTICLES

Impact of Islet Transplantation on Glycemic Control as Evidenced by a Continuous Glucose Monitoring System

Lisa Gorn, D.O.,[1,2] Raquel N. Faradji, M.D.,[1,2] Shari Messinger, Ph.D. ,[1,3] Kathy Monroy, M.D.,[1] David A. Baidal, M.D.,[1] Tatiana Froud, M.D.,[1,4,5] John Mastrototaro, Ph.D.,[6] Camillo Ricordi, M.D.,[1,4] and Rodolfo Alejandro, M.D.[1,2]

Abstract

Background:

This study evaluated the effects of islet allotransplantation (ITx) on metabolic control utilizing a continuous glucose monitoring system (CGMS) and assessed its effectiveness as an indicator and predictor of graft dysfunction (GD).

Methods:

Glycemic control was assessed in 25 patients with type 1 diabetes mellitus (T1DM); 12 ITx recipients and 13 controls. Mean interstitial glucose, standard deviation (SD), glucose variability, and percentage of time in hyperglycemia (%GT >140 mg/dl), hypoglycemia (%GT <54 mg/dl), and normoglycemia (%GT 54–140 mg/dl) were measured in 72-hour time periods from CGMS recordings in the control group at baseline and in the ITx group at 3, 6, 9, 12, 15, and 18 months after ITx completion and were analyzed as predictors and indicators of GD. Hemoglobin A1c (HbA1c), 90-minute glucose after a mixed meal tolerance test, fasting C-peptide/glucose ratio, and insulin requirements were followed.

Results:

Compared to the control group, the percentage of time in hypoglycemia was significantly lower in the ITx group at all time points; time in normoglycemia was increased at all times except at 15 months; and time in hyperglycemia was significantly lower at 6, 9, 12, and 18 months. Mean glucose and glucose variability were significantly lower in the ITx group at all times except at 3 and 15 months, whereas HbA1c and 90-minute glucose were significantly lower in the ITx group at all time points. Mean glucose, SD, glucose variability, and %GT >140 mg/dl were significant as indicators but not as predictors of GD.

continued →

Author Affiliations: [1]Diabetes Research Institute, University of Miami Miller School of Medicine, Miami, Florida; [2]Department of Medicine, [3]Department of Epidemiology, [4]Department of Surgery, and [5]Department of Radiology, University of Miami Miller School of Medicine, Miami, Florida; and [6]Sensors and Implantable Products R&D, Medtronic Diabetes, Los Angeles, California

Abbreviations: (CGMS) continuous glucose monitoring system, (CPGR) C-peptide to glucose ratio, (GD) graft dysfunction, (%GT) percentage of time glucose levels were above, between, or below a certain level, (ITx) islet allotransplantation, (HbA1c) hemoglobin A1c, (SD) standard deviation, (T1DM) type 1 diabetes mellitus

Keywords: continuous glucose monitoring system, diabetes, graft dysfunction, islets, islet transplantation, metabolism

Corresponding Author: Rodolfo Alejandro, M.D., Diabetes Research Institute, 1450 NW 10 Avenue (R-134), Miami, FL 33136; email address *ralejand@med.miami.edu*

Abstract cont.

Conclusions:

The CGMS demonstrated the benefits of ITx in T1DM, with improvements in glycemic control apparent up to 18 months after transplant. CGMS measures were found to be indicators of GD.

J Diabetes Sci Technol 2008;2(2):221-228

Introduction

The Diabetes Control and Complications Trial[1] demonstrated that patients with type 1 diabetes mellitus (T1DM) who were assigned to receive intensive versus conventional insulin therapy had a reduced risk for the development of retinopathy, nephropathy, and neuropathy or had a slowed progression of these complications. They did, however, have a two- to threefold increased risk for severe hypoglycemia. Many patients with T1DM have an impaired counterregulatory response to hypoglycemia,[2] which may lead to episodes of severe hypoglycemia, requiring the assistance of others.

Islet allotransplantation (ITx) may be a therapeutic option for these patients. Since the advent of a steroid-free protocol of immunosuppression, ITx has offered an opportunity for T1DM patients to achieve insulin independence and improved glycemic control, as well as resolution of hypoglycemic events.[3,4] Candidates for this experimental procedure include patients considered to have labile diabetes with hypoglycemia unawareness or poor diabetes control despite intensive insulin therapy. However, the benefits of ITx in reducing or preventing the occurrence of severe hypoglycemic episodes must be weighed carefully against the potential hazards of chronic immunosuppression.[5,6] Islet transplantation can be utilized successfully in patients with T1DM and extreme glycemic lability who cannot maintain adequate control with intensive insulin therapy. Although usually not leading to extended insulin independence, it does have a long-term impact on metabolic stability, with a profound improvement in the number and severity of hypoglycemic episodes.[7]

The initial success of ITx as measured by insulin independence is followed by a decline in functional islet mass, leading to reintroduction of insulin in 60% of recipients at 2 years.[8] The optimal method of assessing graft function is still under debate and requires intensive metabolic testing. The identification of simple predictors of islet dysfunction with a continuous glucose monitoring system (CGMS) may allow early intervention to slow its progression. We previously showed the usefulness of a CGMS as an early indicator of graft dysfunction in a small group of subjects (n = 5) who had undergone ITx.[9] We found that the percentage of time spent above 140 mg/dl was a better indicator of graft dysfunction (GD) than the percentage of time spent above 180 mg/dl. Therefore, for this study we utilized a more stringent definition for hyperglycemia as glucose over 140 mg/dl.

CGMS has been shown to be a useful tool in the assessment of glycemia in patients with type 1 and type 2 diabetes.[10,11] In this study, we explored the use of CGMS to assess glycemic control and success of islet allotransplantation, as well as its utility as an indicator and predictor of GD.

Research Design and Methods

Subjects

From August 2000 until November 2005, 25 T1DM patients who presented to our institution were included in this study: 12 subjects who underwent ITx (ITX group) and 13 islet transplant candidates (control group) who did not undergo transplant. Inclusion criteria were age 18–65, T1DM duration >5 years, negative basal or stimulated C-peptide (<0.3 ng/ml), hypoglycemia unawareness, severe hypoglycemia, and labile diabetes. Informed consent was obtained from all subjects. The studies were approved by the Institutional Review Board.

Subjects in the ITx group required one or two islet infusions to achieve insulin independence. All patients in the ITx group underwent the same transplantation protocol. Of 14 subjects enrolled in this protocol, 12 were included in this analysis. Two patients developed

adverse events related to immunosuppression and were subsequently taken off immunosuppression. Subject characteristics are shown in **Table 1**.

Table 1.
Subject Characteristics[a]

Group	Controls	ITx group
N	13	12
Gender (M/F)	4/9	6/6
Age (years)	49.89 ± 7.48	43.10 ± 8.79
Diabetes duration (years)	30.85 ± 8.47	27.75 ± 12.81
BMI (kg/m^2)	23.63 ± 2.03	24.78 ± 1.88
Time to dysfunction (years)	—	1.49 ± 1.13

[a]Data expressed as mean ± SD

The islet transplantation procedure[12,13] and immunosuppressive regimens for these subjects utilizing daclizumab as induction with sirolimus and tacrolimus maintenance have been described previously elsewhere.[5,12,14]

Definitions

Islet transplant completion was defined as the achievement of insulin independence after sequential islet infusions, usually observed after two islet infusions.

Graft dysfunction was defined as C-peptide-positive ITx recipients with fasting capillary glucose >140 mg/dl and/or 2-hour postprandial glucose >180 mg/dl three or more times in 1 week and/or two consecutive hemoglobin A1c (HbA1c) >6.5% leading to reintroduction of insulin.

Hyperglycemia, normoglycemia, and hypoglycemia were defined as glucose >140, 54–140, and <54 mg/dl, respectively.

Continuous Glucose Monitoring

All subjects underwent one or more 72-hour continuous glucose monitoring periods with the use of the CGMS® System Gold™ from Medtronic MiniMed (Northridge, CA). Subjects in the control group underwent one CGMS monitoring period, whereas subjects in the ITx group underwent multiple monitoring periods at various times after transplant. CGMS tracings were not obtained at baseline and at certain time points in the ITx group as this technology was not yet available. The CGMS[15] involves subcutaneous placement of a flexible glucose sensor designed to remain in place for up to 72 hours, which is then connected to a pager-sized monitoring device that stores glucose data over the same amount of time. The sensor measures interstitial glucose every 10 seconds and provides average glucose values every 5 minutes. Subjects wore the sensor for 72 hours and were instructed to enter four capillary blood glucose values daily into the CGMS for calibration. Data from each 72-hour period were analyzed for mean glucose, standard deviation (SD), glucose variability (absolute value of average measured glucose minus 100 mg/dl), and percentage of time glucose levels were above 140 mg/dl (%GT >140), above 180 mg/dl (%GT >180), between 54 and 140 mg/dl (%GT 54–140), and below 54 mg/dl (%GT <54).

Clinical Assessment

Subjects' weight, body mass index (BMI), and insulin requirements were evaluated at baseline in both groups, as well as every 3 months until 18 months post-ITx in the transplanted group.

Metabolic Testing

Subjects underwent metabolic testing at baseline in both groups and every 3 months until 18 months after transplant in the ITx group. This included HbA1c, C-peptide to glucose ratio (CPGR),[16] and 90-minute glucose from mixed meal tolerance test.

The mixed meal tolerance test was performed after an overnight fast. Subjects ingested 360 ml Boost® High Protein, and samples for glucose and C-peptide were obtained at 0 and 90 minutes.

Plasma glucose concentrations were measured by the hexokinase method. Plasma C-peptide was measured by the double antibody radioimmunoassay (Diagnostics Products Corp., Los Angeles, CA; detection limits: 0.3–5 ng/ml, inter- and intraassay variation coefficients <10%, cross-reactivity with insulin and proinsulin: 20%). Fasting CPGR was calculated as described.[16]

Hemoglobin A1c levels were measured by high-performance liquid chromatography with an automated analyzer (Variant II Hemoglobin Testing System, Bio-Rad, Richmond, CA). Intra- and interassay coefficients of variation were 1.7 and <2.0%, respectively.

Statistical Analysis

For each of the outcome measures under consideration, a linear mixed model regression was fit to data to estimate and compare mean response values during all time points under consideration. This method of analysis generalized linear regression techniques to allow for

repeated observations by taking into account the correlation that exists within observations on the same subject to more appropriately estimate variances used for the various tests of significance. Using this approach, we are able to simultaneously estimate differences between the control group and each posttransplant time point in the ITx group while appropriately accounting for the correlation of outcomes observed within each patient. We also use linear mixed model regression to estimate associations between percentage of time spent in the different glucose level categories and measures of HbA1c, insulin use, CPGR, and 90-minute glucose. CGMS measures were additionally evaluated as predictors and indicators of graft dysfunction with linear mixed model regression. Indication was assessed by comparison of CGMS outcomes between time points where dysfunction was observed and all time points preceding dysfunction. Prediction was assessed by comparison of CGMS outcomes between time points preceding intervals where dysfunction occurred and all prior time points. Results are expressed as means ± SE; a p value <0.05 was considered statistically significant. Analysis was performed using SAS 9.1 software (SAS Institute Inc., Cary, NC).

Results

Demographics and Qualitative Analysis

Twenty-five subjects with T1DM were evaluated: 12 who had undergone ITx (mean age: 43.10 ± 8.79 years; diabetes duration: 27.75 ± 12.81 years; HbA1c: 7.6 ± 0.3%) and 13 controls (mean age: 49.89 ± 7.48 years; diabetes duration: 30.85 ± 8.47 years; HbA1c: 7.5 ± 0.3%). Baseline characteristics were similar between the two groups with the exception of age (p = 0.05) (**Table 1**). Continuous glucose monitoring tracings were obtained in the controls at baseline and at various time points after ITx until 18 months in the transplanted group.

Continuous glucose monitoring system tracings from a transplanted patient showed excellent stability at various times throughout the posttransplant period as compared to a control subject (**Figure 1**).

Continuous Glucose Monitoring System Findings after ITx (Table 2)

The mean interstitial glucose concentration was 139 ± 4.2 mg/dl for the control group. At 3, 6, 9, 12, 15, and 18 months this was 129 ± 3.9, 121 ± 6.1, 119 ± 4.3, 119 ± 5.6, 136 ± 6.7, and 116 ± 3.7 mg/dl, respectively, in the ITx group. These differences were statistically significant at 6, 9, 12, and 18 months post-ITx (p < 0.05) compared to the control group.

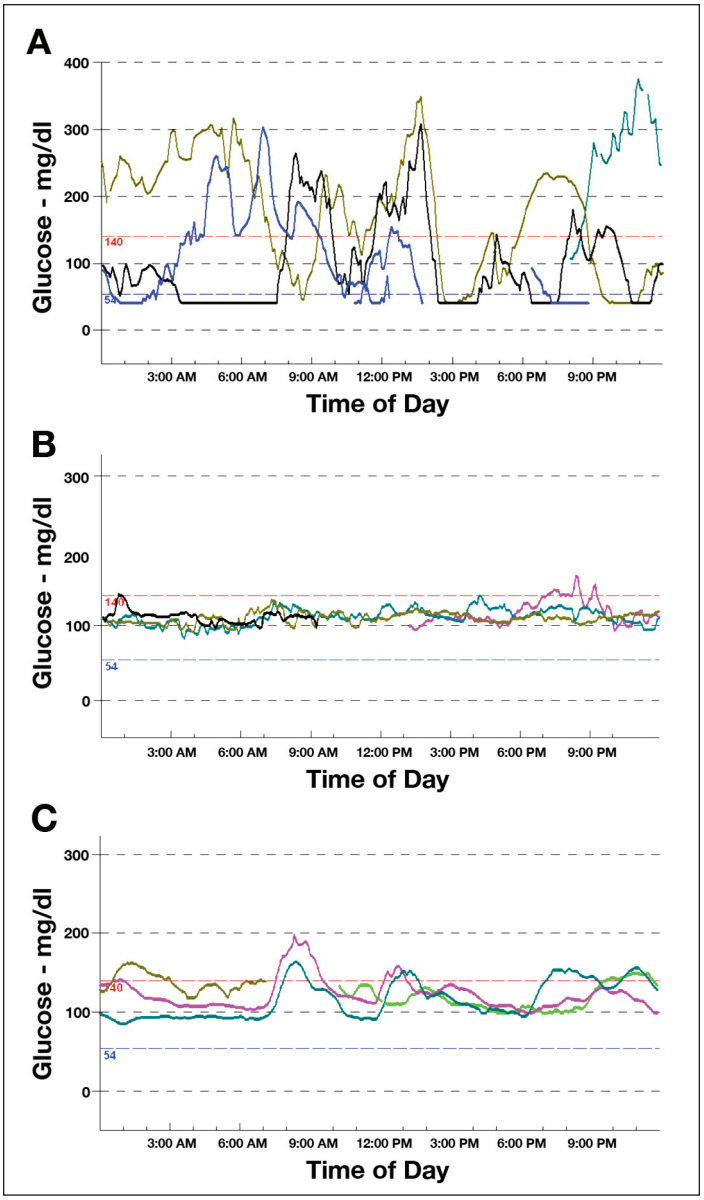

Figure 1. CGMS tracing of a control patient **(A)** and a post-ITx patient 9 months after transplant **(B)** and 18 months after transplant **(C)**. Each colored line represents a different day.

Glucose variability in the control group was 39 ± 3.6 mg/dl. This decreased to 30.6 ± 3.6, 25.2 ± 5.4, 19.8 ± 3.6, 19.8 ± 5.4, 37.8 ± 7.2, and 18 ± 3.6 mg/dl at 3, 6, 9, 12, 15, and 18 months post-ITx, respectively. These differences were statistically significant at all time points except at 3 and 15 months.

Total time spent in hypoglycemia for the control group was 9 ± 2.3%. For the ITx group, this was 0.2 ± 0.18% at 3 months, 2.09 ± 1.08% at 6 months, 2.2 ± 0.73% at 9 months, 1.13 ± 0.4 at 12 months, 1 ± 0.9% at 15 months, and 2.4 ± 1.6% at 18 months. The decreased time spent in hypoglycemia between the ITx group and the control group was statistically significant at all time points (p < 0.05).

Table 2.
CGMS Findings in Control Group versus Transplanted Group at All Time Points after ITx[a]

Group	Controls	ITx 3 months	ITx 6 months	ITx 9 months	ITx 12 months	ITx 15 months	ITx 18 months
N	13	5	11	9	8	8	5
Mean glucose (mg/dl)	139 ± 4	129 ± 4	121 ± 6*	119 ± 4*	119 ± 6*	136 ± 7	117 ± 4*
Glucose variability (mg/dl)	39.6 ± 3.6	30.6 ± 3.6	25.2 ± 5.4*	19.8 ± 3.6*	19.8 ± 5.4*	37.8 ± 7.2	18 ± 3.6*
%GT <54 mg/dl	9 ± 2.3	0.2 ± 0.18*	2.09 ± 1.08*	2.2 ± 0.73*	1.13 ± 0.4*	1 ± 0.9*	2.4 ± 1.6*
%GT 54–140 mg/dl	48.5 ± 2.9	68.8 ± 5.2*	72.5 ± 6.9*	76.6 ± 6.2*	78.8 ± 6.2*	62.4 ± 6.2	80.8 ± 4.2*
%GT >140 mg/dl	42.5 ± 3	31 ± 5.3	25.4 ± 7.2*	21.2 ± 5.7*	20 ± 6.2*	36.6 ± 6.3	16.8 ± 4.4*
%GT >140 mg/dl in insulin-free subjects (*n*)	—	31 ± 5.3 (5)	25.1 ± 7.9 (10)	16 ± 5.9* (6)	11.8 ± 4.9* (6)	37.2 ± 8.8 (5)	13 ± 6.2* (3)

[a]Data expressed as mean ± SEM.
*$p < 0.05$.

There was no association between insulin use and time spent in hypoglycemia in the transplanted group. No patient developed severe hypoglycemia during the study.

Total time spent in normoglycemia in the control group was 48.5 ± 2.9%; in the transplanted group, this was 68.8 ± 5.2, 72.5 ± 6.9, 76.6 ± 6.2, 78.8 ± 6.2, 62.4 ± 6.2, and 80.8 ± 4.2% at 3, 6, 9, 12, 15, and 18 months, respectively. This increase in time spent in normoglycemia between control and ITx groups was statistically significant ($p < 0.05$) at all times except at 15 months post-ITx ($p = 0.051$).

Percentage of time spent in hyperglycemia was 42.5 ± 3% for the control group. In the ITx group, this was 31 ± 5.3, 25.4 ± 7.2, 21.2 ± 5.7, 20 ± 6.2, 36.6 ± 6.3, and 16.8 ± 4.4% at 3, 6, 9, 12, 15, and 18 months, respectively. We found the decrease in time spent in hyperglycemia over 140 mg/dl to be statistically significant at time points 6, 9, 12, and 18 months. There was also a decrease at 3 and 15 months, but this difference did not reach statistical significance (**Figure 2**, **Table 2**). HbA1c values above 6% were associated with an increase in the percentage time spent in hyperglycemia (>140 mg/dl) above 10%, regardless of insulin use.

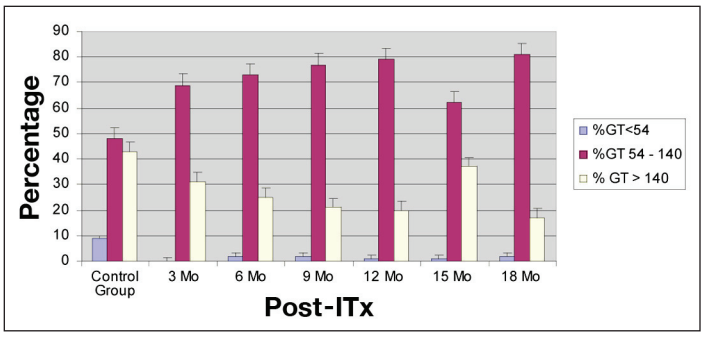

Figure 2. CGMS values for percentage of time spent in hypoglycemia, normoglycemia, and hyperglycemia for the control group versus the transplanted group at all time points post-ITx.

Metabolic Changes after ITx

Comparison of HbA1c, 90-minute glucose, and CPGR showed a significant improvement at all time points after ITx as compared to controls (**Table 3**).

Continuous Glucose Monitoring System as an Indicator of Graft Dysfunction

There are significant differences in metabolic control that occur at the time of GD that can be assessed with use of CGMS. We compared CGMS outcomes measured during intervals where graft dysfunction was observed with those measured at all time points prior to graft dysfunction. Mean glucose, SD, glucose variability, and %GT >140 mg/dl were increased by an estimated 19.38, 15.12, 19.08, and 19.35%, respectively, when GD occurred compared to time points preceding dysfunction (**Table 4**).

Continuous Glucose Monitoring System as a Predictor of Graft Dysfunction

Continuous glucose monitoring system variables were analyzed as predictors of GD by comparison of outcomes measured at time points preceding intervals where graft dysfunction was observed with those measured at time points preceding intervals without dysfunction. By looking at time points preceding the interval where dysfunction occurs, we intended to capture changes in CGMS outcomes that occur just prior to dysfunction so as to be useful as predictive measures. No significant findings were observed for CGMS measures as predictors of GD.

Discussion

Despite efforts to improve glycemic control in T1DM, hypoglycemia remains a major limiting factor, with hypoglycemia unawareness as a marker of risk. Recurrent

Table 3.
Clinical Findings for Control and ITx Groups at All Time Points[a]

Group	Controls	Pre-Tx	ITx 3 months	ITx 6 months	ITx 9 months	ITx 12 months	ITx 15 months	ITx 18 months
N	13	12	5	11	9	8	8	5
HbA1c (%)	7.5 ± 0.3	7.6 ± 0.3	5.5 ± 0.4	5.8 ± 0.1	5.9 ± 0.2	5.9 ± 0.1	6.4 ± 0.2	6 ± 0.1
CPGR (ng/mg)	0.1 ± 0.02	0.1 ± 0.02	1.4 ± 0.2	1.4 ± 0.1	1.7 ± 0.1	1.4 ± 0.1	1.1 ± 0.2	1.4 ± 0.2
90-min glucose (mg/dl)	335 ± 17	361 ± 13	144 ± 12	120 ± 14	158 ± 16	154 ± 19	199 ± 25	160 ± 7
Insulin (IU/kg/day)	0.41 ± 0.04	0.51 ± 0.04	0	0.01 ± 0.01	0.03 ± 0.02	0.03 ± 0.02	0.05 ± 0.02	0.04 ± 0.02
Insulin free	—	—	5	10	6	6	5	3

[a]Data expressed as mean ± SEM. Values at all post-ITx time points were significantly different ($p < 0.05$) than values observed in the control group.

severe hypoglycemia has been found to be more common than isolated episodes.[17] Islet transplantation can be utilized successfully in some T1DM patients who have severe hypoglycemia and hypoglycemia unawareness. Although usually not leading to extended insulin independence, islet transplantation does have a long-term impact on glycemic control, most notably in the reduction in the severity and number of hypoglycemic episodes.[3,18]

Continuous glucose monitoring allows for improved analysis of glucose patterns 24 hours a day. It can provide detailed measurements of interstitial glucose levels for 72-hour periods, but is less accurate than blood glucose measurements. A significant time lag exists between the concentration of glucose in interstitial fluid and blood glucose,[11] and care must be taken when interpreting CGMS readings. We utilized CGMS findings instead of capillary blood glucose to assess mean interstitial blood glucose, SD, and glucose variability, as well as patterns of glycemia.

Table 4.
CGMS Variables Analyzed as Indicators of Graft Dysfunction

CGMS variable	Time points prior to dysfunction (mean)	Time of dysfunction (mean)	Difference ± SE	*p* value
%GT >140 mg/dl	19.23	38.58	19.35 ± 8.59	0.02
%GT >180 mg/dl	3.20	12.14	8.93 ± 4.93	0.07
%GT <54 mg/dl	1.69	1.88	0.19 ± 0.79	0.81
Mean glucose (mg/dl)	117.36	136.74	19.38 ± 8.59	0.02
Standard deviation (mg/dl)	24.39	39.51	15.12 ± 5.65	0.007
Glucose variability (mg/dl)	19.26	38.34	18.9 ± 8.28	0.02

With the use of CGMS in ITx patients and controls with T1DM, we were able to classify the percentage of time spent in hyperglycemia, hypoglycemia, and normoglycemia and found that ITx led to a significant improvement in metabolic control for up to 18 months. A significant reduction in the percentage of time spent in hypoglycemia was observed in the transplanted group at all time points, independent of insulin use. Significant differences were found for time spent in normoglycemia at 3, 6, 9, 12, and 18 months and for time spent in hyperglycemia at 6, 9, 12, and 18 months post-ITx. Possible explanations for increased time spent in hyperglycemia at 3 months could include incomplete islet engraftment and small sample size. At 15 months the increased time spent in hyperglycemia may be secondary to the increased incidence of graft dysfunction, leading to reintroduction of insulin with improved glycemic control by 18 months post-ITx.

CGMS allows for the detection of hypoglycemic events that may be asymptomatic. This study confirms previous findings that persistent islet function even without insulin independence protects against severe hypoglycemia.[3] Kessler and colleagues[19] showed that ITx was as efficient as pancreas transplantation in restoring metabolic control and decreasing blood glucose variability through the use of a subcutaneous CGMS. Paty *et al.*[20] utilized CGMS to evaluate glycemic control in insulin-independent versus insulin-requiring T1DM patients who had undergone ITx and found that both showed improvement compared to nontransplanted patients.

The insulin independence initially achieved after islet transplantation is usually followed by a decline in functional islet mass, with a 75% probability of remaining insulin independent after 1 year.[8] There is no consensus on the optimal method for the assessment of functional islet mass. Most metabolic tests detect graft dysfunction once the damage has already occurred. CGMS has been shown to be a useful tool in the assessment of glycemic control, as well as an early indicator of graft dysfunction.[9] In this larger study we evaluated CGMS as an indicator of graft dysfunction and confirmed that time spent above 140 mg/dl but not above 180 mg/dl was an indicator of graft dysfunction. Time spent above 180 mg/dl likely was not an indicator because patients rarely spend much time above 180 mg/dl prior to intervention with reintroduction of insulin due to frequent self glucose monitoring and strict criteria for diagnosis of graft dysfunction. Mean glucose, SD, and glucose variability were also found to be indicators of graft dysfunction. In addition, we evaluated the ability of CGMS to predict graft dysfunction but were not able to demonstrate that any of these measures are useful as predictors of graft dysfunction.

At the present time, criteria based on finger stick capillary glucose values are utilized to detect and diagnose graft dysfunction. The use of CGMS for a 72-hour period at 3-month intervals, and not more frequently, may have hampered our efforts to capture the events leading up to dysfunction and therefore its prediction.

A limitation of this study is the lack of baseline CGMS tracings in the ITx group, as CGMS became available to us after these patients had been transplanted. Therefore, we chose similarly matched T1DM controls with severe hypoglycemia and hypoglycemia unawareness that were islet transplant candidates.

This study demonstrated the usefulness of CGMS in analyzing the glucose profile of patients with T1DM who have undergone ITx with the ability to detect hypoglycemia that may be asymptomatic. Benefits of ITx up to 18 months posttransplant are apparent, regardless of insulin independence, and include a decrease in the number of hypoglycemic events, maintenance of glucose stability, and an increase in the overall time spent in normoglycemia. CGMS is valuable as an indicator of graft dysfunction with consistent changes in patterns of glycemia observed within 3 months of the diagnosis of graft dysfunction. Further analysis with real-time CGMS and a larger sample size should be carried out in order to assess its value in the early detection and prediction of islet graft dysfunction.

Funding:

This study was supported by National Institutes of Health–National Center for Research Resources [U42-RR16603, GCRC-M01RR16587; NIDDK (R01-DK55347, R01-DK25802); JDRF International (4-2000-946 and 4-2004-361); State of Florida and Diabetes Research Institute Foundation].

Acknowledgments:

Dr. Gorn and Dr. Faradji contributed equally to this work. We thank the staff of the Clinical Islet Transplant Program, the Islet Cell Processing Center, the General Clinical Research Center, the Informatics Core, and Medtronic for their continued support.

Disclosure:

Dr. Mastrototaro is the vice president of sensors and implantable products for Medtronic's diabetes division. Sensors and supplies were donated to us by Medtronic.

References:

1. The Diabetes Control and Complications Trial Research. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329(14):977-86.
2. Rickels MR, Schutta MH, Mueller R, Markmann JF, Barker CF, Naji A, Teff KL. Islet cell hormonal responses to hypoglycemia after human islet transplantation for type 1 diabetes. Diabetes. 2005;54(11):3205-11.
3. Shapiro AM, Ricordi C, Hering BJ, Auchincloss H, Lindblad R, Robertson RP, Secchi A, Brendel MD, Berney T, Brennan DC, Cagliero E, Alejandro R, Ryan EA, DiMercurio B, Morel P, Polonsky KS, Reems JA, Bretzel RG, Bertuzzi F, Froud T, Kandaswamy R, Sutherland DE, Eisenbarth G, Segal M, Preiksaitis J, Korbutt GS, Barton FB, Viviano L, Seyfert-Margolis V, Bluestone J, Lakey JR. International trial of the Edmonton protocol for islet transplantation. N Engl J Med. 2006;355(13):1318-30.
4. Shapiro AM, Lakey JR, Ryan EA, Korbutt GS, Toth E, Warnock GL, Kneteman NM, Rajotte RV. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. N Engl J Med. 2000;343(4):230-8.
5. Froud T, Ricordi C, Baidal DA, Hafiz MM, Ponte G, Cure P, Pileggi A, Poggioli R, Ichii H, Khan A, Ferreira JV, Pugliese A, Esquenazi VV, Kenyon NS, Alejandro R. Islet transplantation in type 1 diabetes mellitus using cultured islets and steroid-free immunosuppression: Miami experience. Am J Transplant. 2005;5(8):2037-46.
6. Poggioli R, Faradji RN, Ponte G, Betancourt A, Messinger S, Baidal DA, Froud T, Ricordi C, Alejandro R. Quality of life after islet transplantation. Am J Transplant. 2006; 6(2):371-8.
7. CITR annual report. 2007.
8. Ryan EA, Paty BW, Senior PA, Bigam D, Alfadhli E, Kneteman NM, Lakey JR, Shapiro AM. Five-year follow-up after clinical islet transplantation. Diabetes. 2005;54(7):2060-9.
9. Faradji RN, Monroy K, Riefkohl A, Lozano L, Gorn L, Froud T, Cure P, Baidal D, Ponte G, Messinger S, Mastrototaro J, Ricordi C, Alejandro R. Continuous glucose monitoring system for early detection of graft dysfunction in allogenic islet transplant recipients. Transplant Proc. 2006;38(10):3274-6.
10. Hay LC, Wilmshurst EG, Fulcher G. Unrecognized hypo- and hyperglycemia in well-controlled patients with type 2 diabetes mellitus: the results of continuous glucose monitoring. Diabetes Technol Ther. 2003;5(1):19-26.

11. Guerci B, Floriot M, Böhme P, Durain D, Benichou M, Jellimann S, Drouin P. Clinical performance of CGMS in type 1 diabetic patients treated by continuous subcutaneous insulin infusion using insulin analogs. Diabetes Care. 2003;26(3):582-9.

12. Geiger MC, Ferreira JV, Hafiz MM, Froud T, Baidal DA, Meneghini LF, Ricordi C, Alejandro R. Evaluation of metabolic control using a continuous subcutaneous glucose monitoring system in patients with type 1 diabetes mellitus who achieved insulin independence after islet cell transplantation. Cell Transplant. 2005;14(2-3):77-84.

13. Ricordi C, Lacy PE, Finke EH, Olack BJ, Scharp DW. Automated method for isolation of human pancreatic islets. Diabetes. 1988;37(4):413-20.

14. Pileggi A, Ricordi C, Kenyon NS, Froud T, Baidal DA, Kahn A, Selvaggi G, Alejandro R. Twenty years of clinical islet transplantation at the Diabetes Research Institute--University of Miami. Clin Transpl. 2004;177-204.

15. Mastrototaro JJ. The MiniMed continuous glucose monitoring system. Diabetes Technol Ther. 2000; 2 Suppl 1:S13-8.

16. Faradji RN, Monroy K, Messinger S, Pileggi A, Froud T, Baidal DA, Cure PE, Ricordi C, Luzi L, Alejandro R. Simple measures to monitor beta-cell mass and assess islet graft dysfunction. Am J Transplant. 2007;7(2):303-8.

17. Pedersen-Bjergaard U, Pramming S, Heller SR, Wallace TM, Rasmussen AK, Jørgensen HV, Matthews DR, Hougaard P, Thorsteinsson B. Severe hypoglycaemia in 1076 adult patients with type 1 diabetes: influence of risk markers and selection. Diabetes Metab Res Rev. 2004;20(6):479-86.

18. Ryan EA, Shandro T, Green K, Paty BW, Senior PA, Bigam D, Shapiro AM, Vantyghem MC. Assessment of the severity of hypoglycemia and glycemic lability in type 1 diabetic subjects undergoing islet transplantation. Diabetes. 2004;53(4):955-62.

19. Kessler L, Passemard R, Oberholzer J, Benhamou PY, Bucher P, Toso C, Meyer P, Penfornis A, Badet L, Wolf P, Colin C, Morel P, Pinget M; GRAGIL Group. Reduction of blood glucose variability in type 1 diabetic patients treated by pancreatic islet transplantation: interest of continuous glucose monitoring. Diabetes Care. 2002;25(12):2256-62.

20. Paty BW, Senior PA, Lakey JR, Shapiro AM, Ryan EA. Assessment of glycemic control after islet transplantation using the continuous glucose monitor in insulin-independent versus insulin-requiring type 1 diabetes subjects. Diabetes Technol Ther. 2006. 8(2): p. 165-73.